






ORIGINAL ARTICLE

Predominant right temporal lobe atrophy: Clinical, neuropsychological and structural differences based on amyloid status

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Abstract

Background: Predominant right temporal atrophy is a radiological sign usually associated with frontotemporal dementia but this sign can also be present in Alzheimer's disease. Given the overlap of clinical symptoms between the two conditions, it is important to know which characteristics allow them to be differentiated.

Objectives: To compare clinical, neuropsychological and structural magnetic resonance imaging (MRI) data of subjects with prominent right anterior temporal atrophy, depending on the status of amyloid biomarkers.

Methods: Among patients followed in the dementia center of Ospedale Maggiore Policlinico, subjects with right anterior temporal atrophy, defined as grade 3 or 4 on the corresponding visual rating scale, were identified. Only subjects with both an MRI scan and amyloid status available were considered. For selected subjects, data were extracted from clinical and neuropsychological records at initial presentation and at last available follow-up. Two raters applied a protocol of eight visual rating scales to compare brain atrophy and white matter hyperintensities.

Results: Of 497 subjects, 17 fulfilled the inclusion criteria: 7 amyloid-positive and 10 amyloid-negative. At initial presentation, executive dysfunction and topographical disorientation were more common in amyloid-positive patients. At follow-up, behavioral symptoms, such as social awkwardness and compulsive attitude, were more frequent in the amyloid-negative patients. Amyloid-positive patients presented an overall worse neuropsychological performance, especially in the language and visuospatial domain, and had higher scores on the right anterior cingulate visual rating scale.

Conclusion: Patients with predominant right temporal atrophy showed clinical, neuropsychological and radiological differences, depending on the status of amyloid biomarkers.

KEYWORDS

Alzheimer's disease, atrophy, biomarkers, frontotemporal dementia, magnetic resonance imaging

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INTRODUCTION

Predominant right temporal atrophy is a radiological sign usually associated with frontotemporal dementia (FTD) [1], a neurodegenerative disorder with heterogeneous clinical and neuropathological features. The clinical picture of FTD can vary from behavioral and personality alterations to various language deficits and encompasses several clinical syndromes: behavioral variant FTD (bvFTD) [2]; the semantic variant of primary progressive aphasia (svPPA) and the non-fluent or agrammatic variant of primary progressive aphasia (nfvPPA) [3]. The typical neuroimaging pattern of bvFTD consists of frontal and/or temporal atrophy [2], whereas svPPA is characterized by asymmetric left anterior temporal atrophy, and nfvPPA shows a pattern of predominant left frontal and insular atrophy [3]. However, an increasing number of studies [1, 4] have described a further differentiated clinicoradiological syndromic variant of FTD, characterized by predominant right temporal lobe atrophy.

Recently, a new diagnostic framework to better study the right temporal variant of FTD (rtvFTD)—long an orphan lacking an organic ontological definition and neglected by diagnostic classifications—has been proposed [5], contributing to the assessment process for this variant. The clinical characteristics of rtvFTD include prosopagnosia, memory deficits, topographical disorientation, and profound behavioral alterations, such as disinhibition and obsessive behaviors [1, 6–9]. The diagnosis is based on the recognition of “core” clinical features, such as prosopagnosia, memory deficits and behavioral changes; “supportive” clinical features, such as speech disturbances and depression; a typical pattern of predominant right anterior temporal lobe atrophy on anatomic or functional neuroimaging and the exclusion of Alzheimer's disease (AD) through the study of amyloid status [5], which is crucial for obtaining the highest diagnostic specificity, considering that the initial presentation of rtvFTD could be confused with AD.

AD typically shows a symmetrical medial temporal and parietal atrophy with amnesic syndrome as the main characteristic; however, three distinct atypical variants have been described [10] and are now included in the diagnostic criteria [11]. The frontal variant of AD [12] shows anterior focal atrophy and behavioral and executive disturbances; the posterior cortical atrophy (PCA) [13] variant shows bilateral parieto-occipital atrophy and visuospatial deficits, whereas the logopenic variant of primary progressive atrophy (lvPPA) [2] presents a left perisylvian region atrophy and language deficits. Completing the topographical variants' framework of AD, the existence of a right

variant of AD (rAD) has been proposed in several studies [14–16]; however, little has been precisely established about its typical clinical presentation.

Preliminary evaluation of the rAD cognitive phenotype highlighted as the most important features amnesic deficit and impairments of cognitive functions lateralized on the right hemisphere, such as attention, constructional apraxia, prosopagnosia and topographical disorientation [17]. In order to distinguish rAD from PCA, the clinical syndrome should be not limited to visuospatial and visuo-perceptual impairments and there must be an asymmetrical right-side pattern of atrophy not confined to the occipital regions [18].

Since right anterior temporal atrophy can be a common feature of rAD and rtvFTD, the objective of this study was to identify clinical, neuropsychological and anatomical differences among subjects with prominent right anterior temporal atrophy, depending on the status of amyloid biomarkers.

METHODS

Patient selection

Of patients followed in the dementia center of Ospedale Policlinico of Milan between 2009 and 2021, those that underwent magnetic resonance imaging (MRI) acquisition with T1 3D volumetric and fluid attenuated inversion recovery (FLAIR) sequences and a confirmation of amyloid status (cerebrospinal fluid [CSF] or positron emission tomography [PET] with florbetapir) were selected ($n=497$). Clinical diagnoses in this group encompassed a number of different neurodegenerative disorders, including AD and FTD, and are based on the current clinical criteria [2, 3, 11, 19].

First, the MRI images were assessed by a neurologist, expert in visual rating scales of atrophy (G.F.) and blind to the demographic and clinical information, who identified subjects with right anterior temporal atrophy, defined as grade 3 or 4 on the anterior temporal atrophy visual rating scale [20–22] (Figure 1). This selection identified 41 patients with a suitable degree of atrophy.

Second, another neurologist (A.A.) and a neuroradiologist (G.C.) reviewed the cohort, to verify predominant right temporal atrophy and to exclude subjects with bilateral temporal atrophy (i.e., patients whose right anterior temporal atrophy grade was not higher by at least one point than the left counterpart in the evaluation of at least

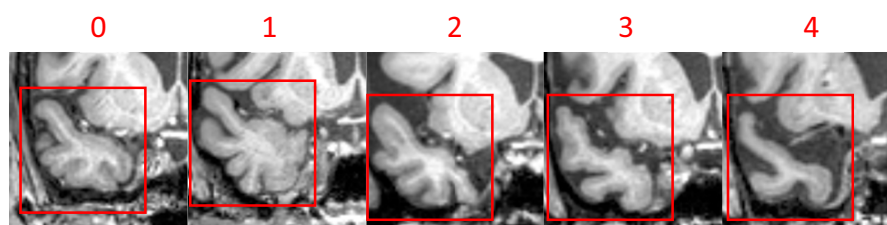


FIGURE 1 Reference images of anterior temporal visual rating scale. 0: Normal appearances (closed sulci); 1: small sulcal slit of anterior temporal sulci; 2: temporal sulci definitely widened; 3: triangular shape of gyri; 4: severe atrophy of temporal pole (convexed sulci).

one rater were excluded). To exclude right temporal atrophy being due to global atrophy, only subjects who had at least one grade higher on the right anterior temporal atrophy visual rating scale than on all other scales were included. After evaluation, 17 patients were enrolled with these criteria (Figure S1).

Amyloid status

CSF samples were collected (by L.P.) in the L3/L4 or L4/L5 interspace and centrifuged at 2000rpm for 10min. The supernatants were aliquoted in polypropylene tubes and stored at -80°C until use. CSF $\text{A}\beta_{1-42}$, phosphorylated tau at threonine 181 (pTau), and total tau (tTau) levels were measured using the ChemiLuminescence Enzyme ImmunoAssay (CLEIA) with a Lumipulse G600II platform (Fujirebio) [23]. We considered, for $\text{A}\beta_{1-42}$, the concentration threshold of 640pg/mL, while for tTau protein this was set at 580pg/mL and for pTau it was 61pg/mL, based on previous studies [23, 24]. Subjects with a CSF concentration greater than this value were considered amyloid-negative (A-), while subjects whose CSF concentration was lower than this number were considered amyloid-positive (A+). Patients showing conflicting results between the CSF $\text{A}\beta_{1-42}$ values and the tTau and pTau levels underwent an amyloid-PET, whose result was considered conclusive as regards the classification belonging to the A- or A+ group.

We interpreted the amyloid-PET results according to the brain amyloid-beta plaque load (BAPL) score. BAPL scores were determined as follows: 1=no β -amyloid load, 2=a minor β -amyloid load and 3=a significant β -amyloid load. Then florbetapir-PET data were qualitatively analyzed by a trained nuclear medicine radiologist using a binary method of interpretation for relating "positive" or "negative" scans to neuropathologically defined categories of amyloid β plaque density.

Clinical data collection

Based on previous studies [1, 5, 18], we identified 30 sets of symptoms, categorized into four macro-domains: cognitive, language, behavioral and other symptoms (see Table 4). Clinical records were retrospectively analyzed for symptoms at "initial presentation" and "last follow-up". All symptoms were recorded as "present" or "absent" for each patient.

In addition, the following data were extracted: demographic features (sex, age at onset, age at end of follow-up, time from disease onset to presentation, education), clinical diagnosis at the time of presentation, measurement of global cognitive function (Mini-Mental State Examination [MMSE] [24]) and family history of any neurodegenerative or psychiatric disease.

Neuropsychological data collection

Neuropsychological examination was performed for diagnostic purposes at first assessment. All subjects underwent at least one

neuropsychological examination in order to assess multiple cognitive functions. In this study we considered the first evaluation and the last follow-up. The standard test battery was composed of: MMSE [25] for global cognitive function; "short story test" for episodic memory [26]; "semantic fluency test" [27], "Boston Naming" [28] or "Sartori's test" [29] for denomination; "digit span backward" [30]; "phonemic fluency" [31]; "Corsi block-tapping test" [30] and "Trail Making Test (TMT) B" [32] for executive functions; "TMT-A", "TMT-BA" [32], "digit span forward" [30] and "attentional matrices" [33] for attention; "clock drawing test" [34] for visuospatial function and "Rey figure copy test" [26] for constructional apraxia.

Visual rating assessment

Two raters applied a protocol composed of eight validated visual rating scales to evaluate brain atrophy on T1 MRI images and white matter hyperintensities on FLAIR sequences. The scales used were: anterior temporal visual rating scale (AT) [22]; medial temporal visual rating scale (MTA) [35]; orbito-frontal rating scale (OF); anterior cingulate rating scale (AC); fronto-insula rating scale (FI) [20]; parietal lobe visual rating scale (PA) [36] and its three components—posterior cingulate sulcus (PCS); precuneus (PRE) and parieto-occipital sulcus (POS) [37]—and Fazekas scales for periventricular and deep white matter hyperintensities [38, 39].

Statistical analysis

The analysis was conducted using Jamovi version 1.8.4. Categorical data were compared using χ^2 tests, while continuous data were compared using *t*-tests. The results of the visual rating scales (i.e., the mean of the scores of the two raters) were compared using an ANOVA test. The reliability of the visual scale protocol was assessed by calculating the Cohen's *K* coefficient of the inter- and intra-rater analysis. The results were thresholded at a *p* value of <0.05 .

RESULTS

Using our inclusion criteria, we identified a sample of 17 patients with right anterior temporal atrophy: 7 with a positive amyloid status (7 CSF) and 10 with a negative amyloid status (7 CSF and 3 PET).

Right temporal atrophy was present in 2.36% of A+ patient (7/296) and in 4.98% of A- (10/201). Prevalences of right temporal atrophy among different syndromes are reported in Table S1.

The sample consisted of 5 female patients (29.4%) and 12 male patients and presented no significant differences in the demographic data based on the gender of the subjects (Table 1).

All subjects were right-handed. Nine patients had a positive family history (52.9%). One patient had a C9ORF72 expansion.

The follow-up had a mean duration of 1.65 years (SD 1.27 years), with a minimum of 4 months and a maximum of 4 years and 5 months.

Comparing the two groups A+ and A- revealed no differences in terms of demographic data. The MMSE at first assessment was significantly higher in the A- cohort (A- 27.70 [SD 2.06] vs. A+ 23.14 [SD 4.02]; $p = 0.008$).

Total-Tau and p-Tau in the CSF did not show a significant difference based on the amyloid status (Table S2).

The clinical diagnoses of the subjects are reported in Table 2.

Among A- patients, in 9 of 10 cases, the diagnosis was behavioral variant frontotemporal dementia (bvFTD) and, in one case, Lewy body dementia. At the end of the follow-up, the average number of fulfilled FTD diagnostic criteria was 2.9 (± 1.29) (Table S3). The A+ group comprised four typical Alzheimer's disease, one frontal variant AD, one PCA and one Lewy body dementia.

Among the subjects with right anterior temporal atrophy predominance, the most common symptoms at onset were amnesic deficit (100%), orientation problems (70.6%), depression (58.8%), apathy/inertia (58.8%) and executive dysfunction (52.9%) (Table 3).

The comparison between A+ and A- showed that, at initial presentation, executive dysfunction was more common in A+ patients (A+ 85.7% vs. A- 30%; $p = 0.024$) and that topographical disorientation was present only in A+ patients (A+ 43% vs. A- 0%; $p = 0.023$) (Figure 2).

At the end of the follow-up (mean length 1.65 years) no other significant association was found between any cognitive symptoms; but regarding behavior, social awkwardness was the prominent symptom in A- patients (70%), alongside obsession (60%) and compulsiveness (40%). Nevertheless, statistical significance was found only for social awkwardness (A- 70% vs. A+ 14.3%; $p = 0.024$). Compulsiveness, present only in amyloid-negative subjects, showed a trend toward significance (A- 40% vs. A+ 0%; $p = 0.056$) (Figure 3).

All 17 subjects underwent the standard battery of neuropsychological tests at the initial presentation, whereas only 8 completed it at last follow up (3 A+ and 5 A-).

At the initial presentation, A+ subjects exhibited a generally worse performance on the neuropsychological tests (Table 4).

Comparing the two groups, we found that A+ patients more commonly showed semantic memory and language deficit: 57.1% had a pathological result in the "phonemic fluency test" (vs. 10% of A-; $p = 0.036$) and 42.8% had a pathological result in the "semantic fluency test" (vs. 0% of A-; $p = 0.028$). None of the A- patients presented a pathological result in the "digit span forward test" (vs. 42.8% of A+; $p = 0.023$).

It is worth noting that the entire cohort of A+ patients presented visuospatial impairments, whereas it was not a common finding in the A- group, as illustrated by outcomes in the "clock drawing test" (A+ 100% vs. A- 22.2%; $p = 0.005$).

TABLE 1 Demographic characteristics of the studied population in total and sorted by amyloid positivity.

Characteristic	N	Total	Amyloid-	Amyloid+	P value
Gender (M:F) (n)	-	12:5	6:4	6:1	0.252
Family history (positive:negative)	-	9:8	5:5	4:3	0.772
Onset age, years (mean \pm SD)	17	71.18 \pm 5.05	71.70 \pm 5.58	70.43 \pm 4.50	0.625
First report age, years (mean \pm SD)	17	74.06 \pm 5.40	74.60 \pm 5.17	73.29 \pm 6.05	0.637
Follow-up, years (mean \pm SD)	17	1.65 \pm 1.27	1.80 \pm 1.40	1.43 \pm 1.13	0.570
Education, years (mean \pm SD)	17	11.18 \pm 5.5	10.00 \pm 5.25	12.86 \pm 5.81	0.307
MMSE1 score (mean \pm SD)	17	25.82 \pm 3.71	27.70 \pm 2.06	23.14 \pm 4.02	0.008
MMSE2 score (mean \pm SD)	15	22.73 \pm 4.45	23.30 \pm 2.71	21.60 \pm 7.09	0.506
MMSE3 score (mean \pm SD)	12	21.42 \pm 5.76	22.00 \pm 4.66	20.25 \pm 8.2	0.643

Note: Bold type denotes statistical significance.

Abbreviations: F, female; M, male; MMSE, Mini-Mental State Examination; SD, standard deviation.

TABLE 2 Clinical diagnosis of the studied population in total and sorted by amyloid positivity.

Diagnosis	N	%	AMYL- (n)	AMYL- (%)	AMYL+ (n)	AMYL+ (%)
Behavioral variant FTD (bvFTD)	9	52.9	9	90	0	0
Alzheimer's disease	4	23.5	0	0	4	57.1
Alzheimer's disease, frontal variant	1	5.9	0	0	1	14.3
Posterior cortical atrophy	1	5.9	0	0	1	14.3
Lewy body dementia	2	11.8	1	10	1	14.3
Total	17	100	10	100	7	100

Abbreviations: AMYL-, right temporal amyloid-negative; AMYL+, right temporal amyloid-positive; FTD, frontotemporal dementia.

TABLE 3 Frequencies of clinical characteristics' presentation of the studied population sorted by amyloid positivity at the beginning and at the end of the follow-up.

Clinical features	Initial presentation (% of total)			Last follow-up (% of total)		
	AMYL-	AMYL+	χ^2 test (p value)	AMYL-	AMYL+	χ^2 test (p value)
Cognitive						
Amnesic deficit	100	100	–	100	100	–
Prosopagnosia	10	42.8	0.116	30	71.4	0.092
Executive dysfunction	30	85.7	0.024	60	85.7	0.252
Orientation problem	60	85.7	0.252	80	85.7	0.761
Topographical disorientation	0	42.8	0.023	10	42.8	0.116
Visuospatial problems	20	42.8	0.309	50	57.1	0.772
Apraxia	30	28.6	0.949	70	42.8	0.263
Calculation deficit	0	14.3	0.218	10	14.3	0.787
Concentration deficit	30	28.6	0.949	60	28.6	0.201
Language						
Word-finding deficit	30	42.8	0.585	60	42.8	0.486
Single word comprehension deficit	0	0	–	10	14.3	0.787
Denomination deficit	10	14.3	0.787	50	28.6	0.377
Object knowledge deficit	0	14.3	0.218	0	14.3	0.218
Alexia	0	0	–	0	0	–
Agraphia	0	0	–	0	0	–
Behavior						
Disinhibition	10	14.2	0.696	30	14.3	0.452
Social awkwardness	20	14.2	0.761	70	14.3	0.024
Irascibility	10	42.8	0.116	10	42.8	0.116
Childishness	0	0	–	0	0	–
Apathy/inertia	60	57.1	0.906	60	57.1	0.906
Loss of empathy	10	0	0.388	20	0	0.208
Obsessions	40	14.3	0.252	60	42.8	0.486
Compulsiveness	20	0	0.208	40	0	0.056
Personal taste changes	0	0	–	0	0	–
Hyperorality	20	14.2	0.761	40	43.8	0.906
Loss of insight	10	28.6	0.375	30	28.6	0.949
Other						
Hyper-religiosity	0	0	–	10	0	0.388
Depression	60	57.1	0.906	40	42.8	0.906
Anxiety/panic	50	14.3	0.129	30	28.6	0.949
Sleep disturbances	40	28.6	0.627	30	14.3	0.452

Note: Bold type denotes statistical significance.

Abbreviations: AMYL-, right temporal amyloid-negative; AMYL+, right temporal amyloid-positive.

No significant difference was noted at the end of the follow-up between the two groups.

The only significant difference in visual rating scales was the right anterior cingulate scale, in which A+ subjects had a higher score (A+ 2.00 vs. A- 1.05; $p = 0.050$) (Table S4).

DISCUSSION

Right temporal lobe atrophy is a radiological sign shared by different variants of common neurological syndromes, such as rtvFTD and the preliminary and evolving descriptions of rAD. In this study, we

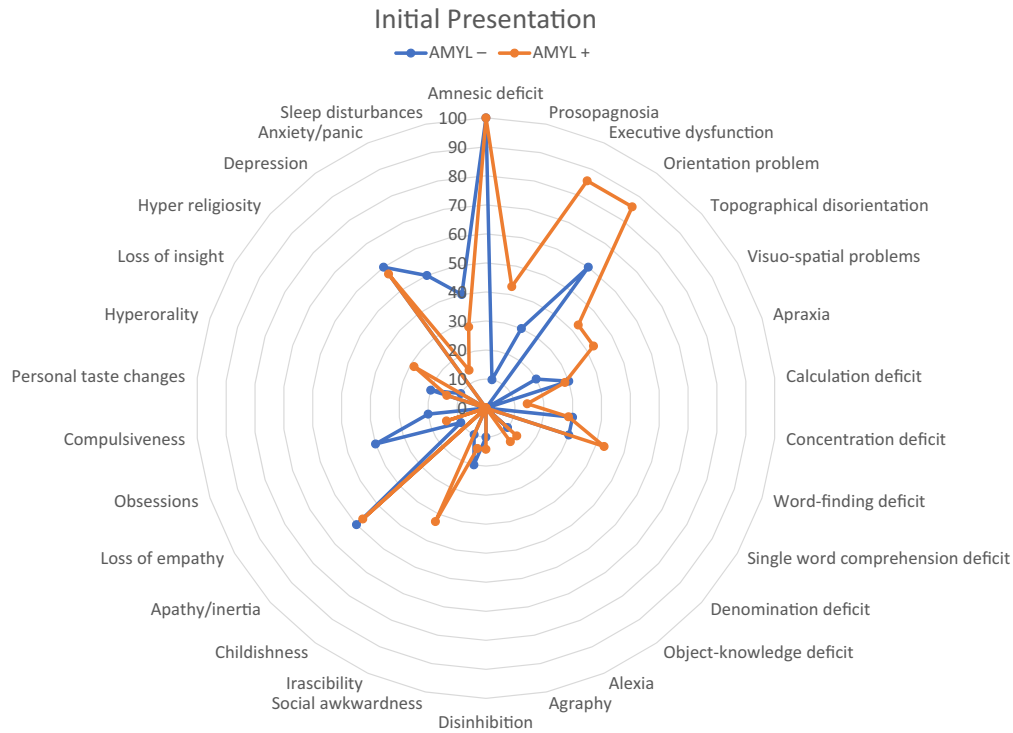


FIGURE 2 Main clinical differences among amyloid groups at the beginning of the follow-up. AMYL-, right temporal amyloid-negative; AMYL+, right temporal amyloid-positive.



FIGURE 3 Main clinical differences among amyloid groups at end of follow-up. AMYL-, right temporal amyloid-negative; AMYL+, right temporal amyloid-positive.

TABLE 4 Frequencies of pathological results at the neuropsychological tests in the studied population sorted by amyloid positivity at the beginning and at the end of the follow-up.

Neuropsychological tests		Pathological test initial presentation (percentage of total)			Pathological test last follow-up (percentage of total)		
Cognitive domain	Test	AMYL-	AMYL+	χ^2 test (p value)	AMYL-	AMYL+	χ^2 test (p value)
Episodic memory	Short story test	71.4	66.7	0.853	50	75	0.465
Short-term memory	Corsi block-tapping test	11.1	16.7	0.756	16.7	33.3	0.571
Language	Denomination test	30	66.7	0.154	28.6	75	0.137
	Semantic fluency test	0	42.8	0.029	28.6	50	0.477
Executive function	Digit span backward	10	14.3	0.787	14.3	25	0.658
	Phonemic fluency test	10	57.1	0.036	42.8	50	0.819
	TMT-B	44.4	66.7	0.398	57	50	0.819
Attention	Attentional matrices	20	14.3	0.761	28.6	25	0.898
	Digit span forward	0	42.8	0.023	0	25	0.165
	TMT-A	20	42.8	0.309	42.8	50	0.819
	TMT-BA	50	80	0.279	66.7	66.7	1
Visuospatial	Clock drawing	22.2	100	0.005	40	66.7	0.465
Apraxia	Rey figure copy	42.8	66.7	0.391	60	33.3	0.465

Note: Bold type denotes statistical significance.

Abbreviations: AMYL-, right temporal amyloid-negative; AMYL+, right temporal amyloid-positive; TMT, Trail Making Test.

retrospectively identified 17 patients with both predominant right anterior temporal atrophy and confirmation of their amyloid-status (CSF or amyloid-PET) and then built a complete clinical, neuropsychological and neuroradiological profile to compare subjects, depending on amyloid status.

Analysis of the clinical reports showed, aside from the ubiquitous presence of reported amnesic syndrome, a distinction between the two groups. Behavioral symptoms, such as social awkwardness and compulsive attitude, were more frequent in the amyloid-negative patients only at the end of follow-up: those differences could be explained by a discrepancy in frontal atrophy, associated with FTD but not with typical AD or the still-evolving definition of rAD. While apathy was common in both groups, the loss of empathy, associated with the right frontotemporal areas [6, 40], was found in very few subjects in either group.

The amyloid-positive subjects, on the other hand, presented cognitive symptoms such as topographical disorientation and executive dysfunctions more often; topographical disorientation was present only in the amyloid-positive group. The findings of the impairment of these right-lateralized functions are consistent with the conclusions of other studies about cases of AD with asymmetric right predominant atrophy [14, 16, 41, 42].

It is worth noting that there was no statistically significant difference in the occurrence of prosopagnosia, a symptom that has characteristically been associated with involvement of the right temporal lobe [1, 4, 43] and considered a main feature of rtvFTD. In our records though, prosopagnosia was more common in the amyloid-positive cohort, both at the beginning and at the end of

follow-up. In total, 47.1% of our patients showed prosopagnosia (30% of A- and 71.4% of A+): a lesser percentage than found in other studies involving similar subjects, which ranged between and around 60% and 90% [1, 4, 5, 44]. This discrepancy could be explained by the retrospective nature of the present study: prosopagnosia is not a common and known symptom, and patients and/or caregivers might confuse it with undefined memory problems, so it could easily be missed if not investigated promptly by a clinician. Moreover, the concept of prosopagnosia in rtvFTD is under discussion as it is more likely a deficit in person recognition rather than just face recognition.

Episodic memory impairment, as previously noted, was reported in every patient examined but this was not always confirmed by pathological results in specific tests. We expected that episodic memory deficit would have been more common in the amyloid-positive cohort, but no difference was found among the two groups. This may be due to the fact that rtvFTD [5, 45] can present an amnesic syndrome more commonly than bvFTD.

The neuropsychological tests administered at the initial presentation showed that amyloid-positive patients performed worse specifically in the language and visuospatial domains and generally worse neuropsychologically. The language impairments, documented by the phonemic and semantic fluency tests, did not, however, come with any radiological confirmation: the scores obtained with the visual rating scale used to assess the various language zones of the left hemisphere were comparable between the two groups. It is worth noting that no subject had a diagnosis of svPPA: this could be explained by our enrollment criteria and

the exclusion of patients with left temporal or bilateral temporal atrophy.

Moreover, a divergence in the occurrence of language deficit emerged when comparing clinical reports and neuropsychological test results: this could be explained by considering that the standardized approach of the neuropsychological test could more precisely evaluate a symptom than the initial clinical interrogation. The same could be said for the prevalence of complaints about memory deficit by patient and/or caregiver, reported for every patient evaluated, as well as the pathological results of the neuropsychological test assessing the memory domain, which was not universal.

At the end of the follow-up, the neuropsychological reports showed a progressive worsening of the A- patients' performance and the consequent loss of all statistical significance in the comparison of the two groups: considering the drop in the tests taken and the overall more-compromised subjects, it was a result we expected.

We could not find any differences in t Tau and p Tau based on the amyloid status. This could be explained by the procedure that we used to settle the conflicting results between the CSF biomarkers, as this was based on amyloid-PET results.

The correct classification of patients with right temporal atrophy is still not fully certain. The predominant right temporal atrophy has often been associated with variants of FTD, but our study suggested that other clinical syndromes could be associated with this radiological sign, such as AD and Lewy body dementia, as displayed by some of our patients. Due to the lack of pathological records for our subjects, it is not possible to know whether the amyloid positivity with biomarkers represents a co-pathology FTD-AD or simply represents a part of the AD continuum. Furthermore, the exact clinical phenotype associated with right temporal atrophy is not unequivocal: many of our patients shared common characteristics, even if their diagnoses were very different.

All this implies the need to enlarge the diagnosis spectrum of right temporal atrophy, which should not be considered an exclusive feature of FTD. In particular, considering cases of extrapyramidal syndromes, it is important to point out that, in the present case series, diagnoses were based on clinical characteristics, as this would imply a further broadening of the spectrum of possible presentation of this radiological pattern.

The clinical and radiological overlap highlighted by our results makes it difficult to clinically distinguish *rtv*FTD and AD without the confirmation of amyloid status. Even with that validation, the exclusion of an AD co-pathology in the clinical presentation of amnesic syndrome and prosopagnosia cannot be made reliably, as other studies have suggested [46].

The features associated with amyloid-positive status in our study, however, seemed to follow the same direction as the ongoing attempt to describe and present the right variant of AD, whose characteristics, which while they may be common to *rtv*FTD, are yet to be fully and precisely determined.

To identify and recognize an *rAD* variant is a complex task because of the different recognizability that right-lateralized symptoms

have compared to disturbances of language, an almost exclusively left-lateralized phenomenon. Language impairments are easily recognizable, even by the patient or caregiver, whereas deficits in visuospatial or attention functions may be more subtle and difficult to identify [14]. Moreover, it has been shown that right-lateralized functions are also partly influenced by the left hemisphere, and thus the impact of the asymmetric right hemisphere atrophy could be compensated for by the contralateral area [47].

Many previous studies have tried to identify and frame *rAD* [16–18, 40, 41, 48]. In 2021, a preliminary definition of the variant was proposed, whose main clinical characteristics were: topographical disorientation, constructive apraxia, prosopagnosia, and anterograde amnesia with low frequency of language or behavioral symptoms in the early stages. The radiological features were right predominant atrophy in the temporal and parietal lobes. Our data could support this definition: the clinical and neuropsychological features associated with amyloid positivity in our cohort of right temporal atrophy patients could be linked to what has been highlighted in other studies on *rAD*.

The importance of correct classification of these (although uncommon) cases will become of paramount importance when considering amyloid-targeted therapy, as access to drugs might not be immediate based on a radiological presentation not associated with the more frequent atrophic patterns of AD. In the light of new pharmacological opportunities, with the approval of anti-amyloid drugs as treatments for AD, this could already have an immediate impact. The possibility that patients with predominant right temporal atrophy have AD should not be ruled out a priori, and an increasingly precise definition of asymmetrical presentation of AD could, therefore, be helpful in daily and future clinical practice.

The present study, however, has some limitations. In the selection process we intended to include all the subjects with right temporal atrophy, independently from the clinical diagnosis, but at the same time we did not want to be overinclusive with the subjects that had right temporal atrophy in the context of global atrophy. Nevertheless patients could show some degree of atrophy in the frontal or parietal lobes but still the right anterior temporal lobe had to be more affected. Due to the retrospective nature of the work, some useful clinical information such as agnosia or hyper-religiosity may have been missed because it was not specifically investigated. The clinical interviewer's focus on some peculiar and rare symptoms, such as prosopagnosia or changes of personal taste, may not have been the ideal approach for this study. Moreover, the follow-up was heterogeneous for the different subjects, and there was no pathological confirmation of the diagnoses. Another limitation is the use of visual rating scales instead of a voxel-based volumetric analysis to assess the atrophy pattern. Finally, the number of enrolled subjects was low, and therefore larger, multicentric and prospective studies in this area are needed to further clarify and describe right temporal atrophy patients, depending on biomarker positivity.

CONCLUSIONS

This study suggests that predominant right temporal atrophy may be shared by variants of different syndromes, and the associated clinical and neuropsychological phenotype may vary depending on the positivity of the amyloid biomarkers. Right anterior temporal atrophy was associated with cognitive symptoms, such as topographical disorientation and executive dysfunctions, in the amyloid-positive cohort, whereas behavioral symptoms were more frequent in amyloid-negative patients.

AUTHOR CONTRIBUTIONS

Jacopo Di Napoli: Writing – original draft; data curation; formal analysis; writing – review and editing. **Andrea Arighi:** Methodology; investigation; formal analysis. **Giorgio Conte:** Methodology; investigation; formal analysis. **Tiziana Carandini:** Investigation. **Luca Sacchi:** Investigation. **Marina Arcaro:** Investigation. **Chiara Fenoglio:** Investigation. **Federica Sorrentino:** Investigation. **Matteo Mercurio:** Investigation. **Anna M. Pietroboni:** Investigation. **Giulia Giardinieri:** Investigation. **Fabio Triulzi:** Supervision. **Daniela Galimberti:** Supervision; writing – review and editing; funding acquisition. **Elio Scarpini:** Supervision; funding acquisition. **Giorgio G. Fumagalli:** Conceptualization; investigation; formal analysis; methodology; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

This study was approved by the local ethical committee on human studies and written informed consent was obtained from all subjects.

CONSENT FOR PUBLICATION

Not applicable.

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