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Il ruolo potenziale dei biomarcatori liquorali nella diagnosi e nella terapia delle afasie primarie progressive

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INTRODUZIONE

Afasia primaria progressiva (PPA): sindrome clinica caratterizzata da deficit selettivo e progressivo a carico del linguaggio su base neurodegenerativa.

La PPA è suddivisa in tre varianti:

- Variante Logopenica (lvPPA, *logopenic variant of PPA*)

- Variante Non fluente/agrammatica (nfvPPA, *non fluent/agrammatic variant of PPA)*

- Variante Semantica (svPPA, *semantic variant of PPA*)

La svPPA e la nfvPPA sono classificate tra le forme di demenza fronto-temporale (FTD, *fronto-temporal dementia*), mentre la lvPPA è stata associata alla malattia di Alzheimer (AD, *Alzheimer disease*) di cui condivide i meccanismi patogenetici, come dimostrato da recenti studi clinico-patologici; pertanto, l'analisi dei biomarcatori liquorali dell'AD, quali beta amiloide-42 (Aβ42), tau (tau) e tau fosforilata (p-tau), potrebbe rivelarsi un utile strumento nella diagnosi differenziale delle PPA.

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Alzheimer's pathology in primary progressive aphasia

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Abstract

Primary progressive aphasia (PPA) is a neurodegenerative disorder with language impairment as the primary feature. Different subtypes have been described and the 3 best characterized are progressive nonfluent aphasia (PNFA), semantic dementia (SD) and logopenic/phonological aphasia (LPA). Of these subtypes, LPA is most commonly associated with Alzheimer's disease (AD) pathology. However, the features of PPA associated with AD have not been fully defined. Here we retrospectively identified 14 patients with PPA and either pathologically confirmed AD or cerebrospinal fluid (CSF) biomarkers consistent with AD. Analysis of neurological and neuropsychological features revealed that all patients had a syndrome of LPA with relatively nonfluent spontaneous speech, phonemic errors, and reduced digit span; most patients also had impaired verbal episodic memory. Analysis of the pattern of cortical thinning in these patients revealed left posterior superior temporal, inferior parietal, medial temporal, and posterior cingulate involvement and in patients with more severe disease, increasing involvement of left anterior temporal and frontal cortices and right hemisphere areas in the temporo-parietal junction, posterior cingulate, and medial temporal lobe. We propose that LPA may be a "unihemispheric" presentation of AD, and discuss this concept in relation to accumulating evidence concerning language dysfunction in AD.

Keywords: Frontotemporal dementia; Frontotemporal lobar degeneration; Primary progressive aphasia; Logopenic aphasia; Progressive nonfluent aphasia; Alzheimer's disease

Classification of primary progressive aphasia and its variants

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ABSTRACT

This article provides a classification of primary progressive aphasia (PPA) and its 3 main variants to improve the uniformity of case reporting and the reliability of research results. Criteria for the 3 variants of PPA—nonfluent/agrammatic, semantic, and logopenic—were developed by an international group of PPA investigators who convened on 3 occasions to operationalize earlier published clinical descriptions for PPA subtypes. Patients are first diagnosed with PPA and are then divided into clinical variants based on specific speech and language features characteristic of each subtype. Classification can then be further specified as "imaging-supported" if the expected pattern of atrophy is found and "with definite pathology" if pathologic or genetic data are available. The working recommendations are presented in lists of features, and suggested assessment tasks are also provided. These recommendations have been widely agreed upon by a large group of experts and should be used to ensure consistency of PPA classification in future studies. Future collaborations will collect prospective data to identify relationships between each of these syndromes and specific biomarkers for a more detailed understanding of clinicopathologic correlations. **Neurology® 2011;76:1006–1014**

GLOSSARY

AD = Alzheimer disease; **FTLD** = frontotemporal lobar degeneration; **PPA** = primary progressive aphasia.

A progressive disorder of language associated with atrophy of the frontal and temporal regions of the left hemisphere was first described in the 1890s by Pick[1] and Serieux.[2] In the modern literature, Mesulam[3] described a series of cases with "slowly progressive aphasia," subsequently renamed primary progressive aphasia (PPA).[4] Warrington[5] described a progressive disorder of

* **Criteri di inclusione e esclusione per la diagnosi di Afasia Primaria Progressiva**

* **Criteri di inclusione: i criteri 1-3 devono essere presenti**
* 1. La principale manifestazione clinica è una difficoltà del linguaggio
* 2. Questi deficit sono la principale causa della compromissione delle ADL
* 3. L'afasia deve essere il deficit prominente all'esordio e nelle fasi iniziali di malattia
* **Criteri di esclusione: i criteri 1-4 devono essere assenti**
* 1. Il quadro è spiegato da altre malattie del SNC non degenerative o da altra condizione medica
* 2. Il disturbo cognitivo è riconducibile ad una malattia psichiatrica
* 3. Prevalente compromissione della memoria episodica, della memoria visiva e delle funzioni visuo-spaziali
* 4. Prevalente e iniziale disturbo del comportamento

Table 2 Diagnostic features for the nonfluent/agrammatic variant PPA

I. Clinical diagnosis of nonfluent/agrammatic variant PPA
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge
II. Imaging-supported nonfluent/agrammatic variant diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant left posterior fronto-insular atrophy on MRI or
b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET
III. Nonfluent/agrammatic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Abbreviations: AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia.

Table 3 Diagnostic criteria for the semantic variant PPA

I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)
II. Imaging-supported semantic variant PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
a. Predominant anterior temporal lobe atrophy
b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET
III. Semantic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

Abbreviations: AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia.

thology does not imply that the clinical syndrome is better defined clinically, but only that it has been

Table 4 Diagnostic criteria for logopenic variant PPA

I. Clinical diagnosis of logopenic variant PPA
Both of the following core features must be present:
1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases
At least 3 of the following other features must be present:
1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism
II. Imaging-supported logopenic variant diagnosis
Both criteria must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
a. Predominant left posterior perisylvian or parietal atrophy on MRI
b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
III. Logopenic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other)
3. Presence of a known pathogenic mutation

Abbreviations: AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia.

Caratteristiche della afasie primarie progressive

Variante non fluente della PPA

- Agrammatismo con errori nella produzione del linguaggio
- Linguaggio esitante e sforzato con distorsioni di suoni e fonemi
- 2 o più dei seguenti: deficit nella comprensione di frasi sintatticamente complesse; risparmio della comprensione della singola parola; risparmio della conoscenza dell'oggetto

Variante semantica della PPA

- Compromissione della denominazione
- Compromissione della comprensione della singola parola
- 3 o più dei seguenti: compromissione della conoscenza dell'oggetto (specie se poco familiare); dislessia di superficie o disgrafia; risparmio della ripetizione; risparmio della produzione linguistica (in termini di grammatica e produzione di parole)

Variante logopenica della PPA

- Compromissione del recupero della singola parola nel linguaggio spontaneo e nella prova di denominazione
- Compromissione della ripetizione di sentenze o frasi
- 3 o più delle seguenti: errori fonologici nel linguaggio spontaneo e nella prova di denominazione; risparmio della comprensione della singola parola e della conoscenza dell'oggetto; risparmio dell'aspetto motorio del linguaggio; assenza di agrammatismo

Primary progressive aphasia: clinicopathological correlations

Murray Grossman

Abstract | Primary progressive aphasia (PPA) is a disorder of declining language that is a frequent presentation of neurodegenerative diseases such as frontotemporal lobar degeneration. Three variants of PPA are recognized: progressive nonfluent aphasia, semantic dementia, and logopenic progressive aphasia. In an era of etiology-specific treatments for neurodegenerative conditions, determining the histopathological basis of PPA is crucial. Clinicopathological correlations in PPA emphasize the contributory role of dementia with Pick bodies and other tauopathies, TDP-43 proteinopathies, and Alzheimer disease. These data suggest an association between a specific PPA variant and an underlying pathology, although many cases of PPA are associated with an unexpected pathology. Neuroimaging and biofluid biomarkers are now emerging as important adjuncts to clinical diagnosis. There is great hope that the addition of biomarker assessments to careful clinical examination will enable accurate diagnosis of the pathology associated with PPA during a patient's life, and that such findings will serve as the basis for clinical trials in this spectrum of disease.

Grossman, M. *Nat. Rev. Neurol.* **6**, 88–97 (2010): doi:10.1038/nrneurol.2009.216

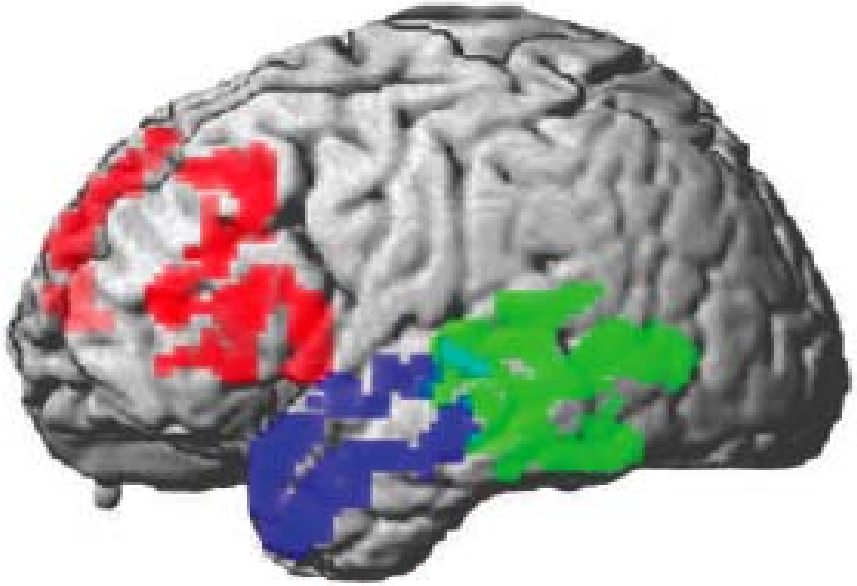

Figure 5 | Distribution of cortical atrophy in three primary progressive aphasia syndromes. This image is based on a quantitative cortical thickness analysis of high-resolution 3T MRI studies[129] in patients with primary progressive aphasia. Statistically significant cortical thinning is observed in inferior, dorsolateral prefrontal and insular regions of the left frontal lobe in progressive nonfluent aphasia (red, $n = 12$ patients), in the left lateral temporal and inferior parietal regions in logopenic progressive aphasia (green, $n = 9$ patients), and in the left anterior temporal lobe in semantic dementia (blue, $n = 11$ patients) relative to age-matched healthy adults.

Grossman, M. *Nat. Rev. Neurol.* 6, 88–97 (2010):

MATERIALI E METODI

Abbiamo confrontato le concentrazioni liquorali di Aβ42, tau e p-tau in un campione di 14 pazienti con diagnosi di PPA, divisi in due gruppi: nel primo abbiamo incluso 7 pazienti con lvPPA, nel secondo 7 pazienti affetti da svPPA o nfvPPA. I dosaggi liquorali sono stati effettuati utilizzando kits ELISA (Innogenetics, Ghent, Belgium).

PAZIENTI

	N	ETA' (min-max)	MMSE (min-max)	SCOLARITA' (min-max)	DURATA (MESI)
lv-PPA	7	68 (56-77)	19 (13-22)	11 (5-13)	41 (12-65)
sv/nfv-PPA	7	69 (58-80)	22 (9-28)	10 (5-19)	33 (18-60)

RISULTATI

* ***Valori normativi dei biomarcatori liquorali in letteratura***

Biomarcatore	Valori normativi
Aβ42	>500 *
Tau	<500 **
p-Tau	<61 ***

** Sjogren et al., Clin Chem (2001)*

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Hansson et al., Lancet Neurol (2006)

lvPPA

PAZIENTE	BETA-AMILOIDE 42	TAU	TAU FOSFORILATA
lvPPA 1	199*	839*	125*
lvPPA 2	241*	262	64*
lvPPA 3	550	526*	132*
lvPPA 4	571	876*	152*
lvPPA 5	350*	999*	154*
lvPPA 6	404*	280	49
lvPPA 7	325*	582*	87*

sv/nfvPPA

PAZIENTE	BETA-AMILOIDE 42	TAU	TAU FOSFORILATA
svPPA 1	1079	129	38
nfvPPA 2	367*	555*	59
nfvPPA 3	744	552*	47
nfvPPA 4	937	165	39
nfvPPA 5	1229	289	73*
nfvPPA 6	557	132	37
nfvPPA 7	984	295	61

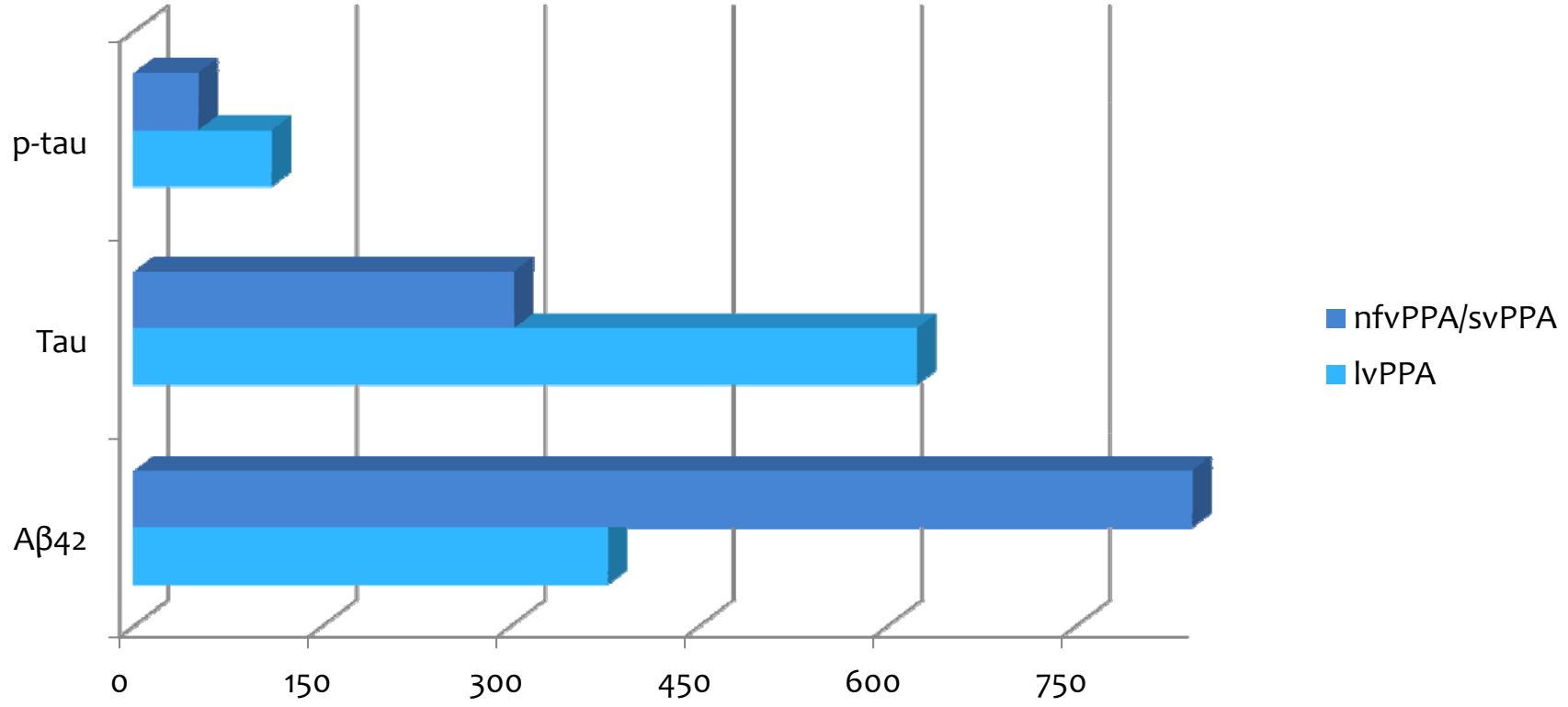
RISULTATI

* ***I marcatori liquorali nelle varianti di PPA***

	lvPPA	svPPA/nfvPPA
Aβ42 media [± DS]	**377** [± 142,5] pg/ml	**842** [± 303,2] pg/ml
Tau media [± DS]	**623** [± 291,9] pg/ml	**302** [± 184,5] pg/ml
p-Tau media [± DS]	**109** [± 42,4] pg/ml	**50,6** [± 14] pg/ml

RISULTATI

* ***I marcatori liquorali nelle varianti di PPA***



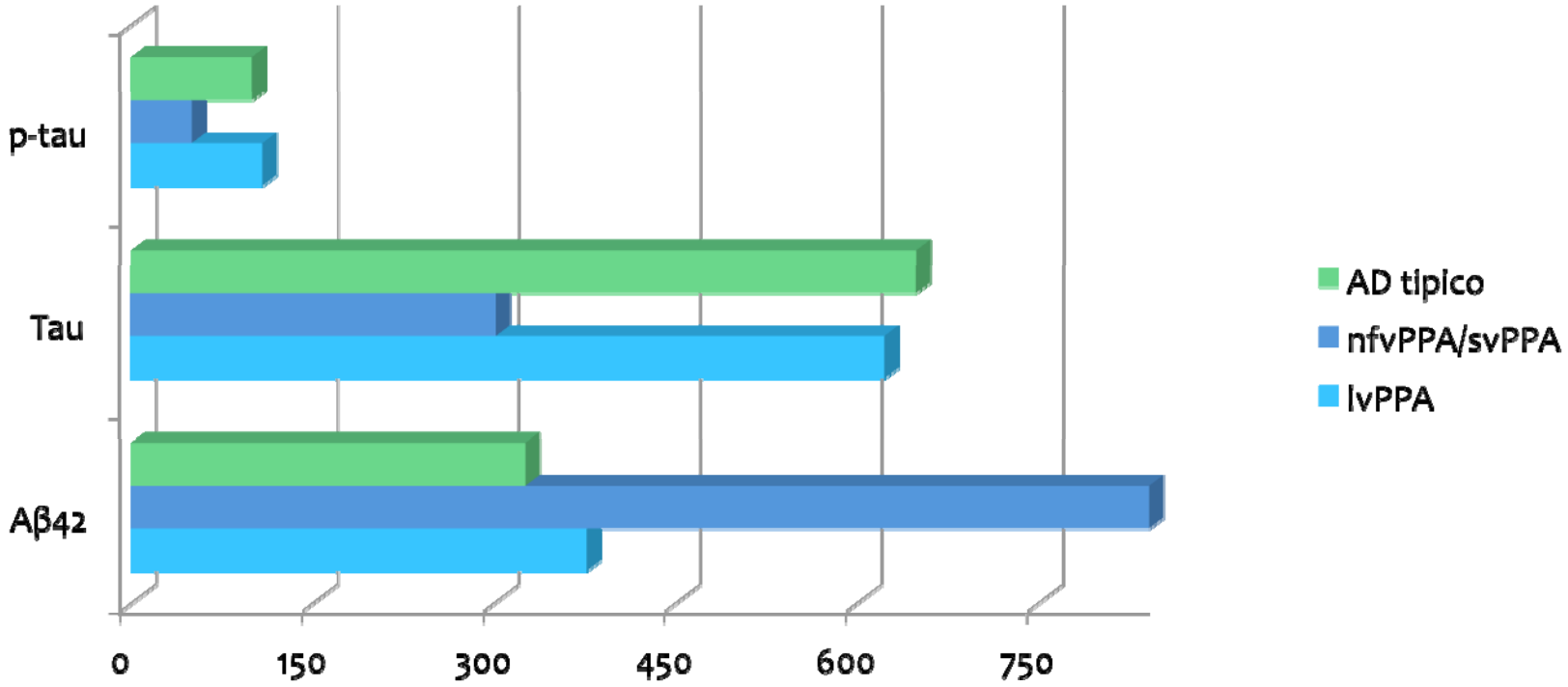
RISULTATI

* ***Confronto con malattia di Alzheimer ad esordio «tipico»***

	lvPPA	svPPA/nfvPPA	AD tipico
Aβ42 media [± DS]	**377** [± 142,5] pg/ml	**842** [± 303,2] pg/ml	**327** [± 166] pg/ml
Tau media [± DS]	**623** [± 291,9] pg/ml	**302** [± 184,5] pg/ml	**649,5** [± 370,1] pg/ml
p-Tau media [± DS]	**109** [± 42,4] pg/ml	**50,6** [± 14] pg/ml	**100,4** [± 40,5] pg/ml

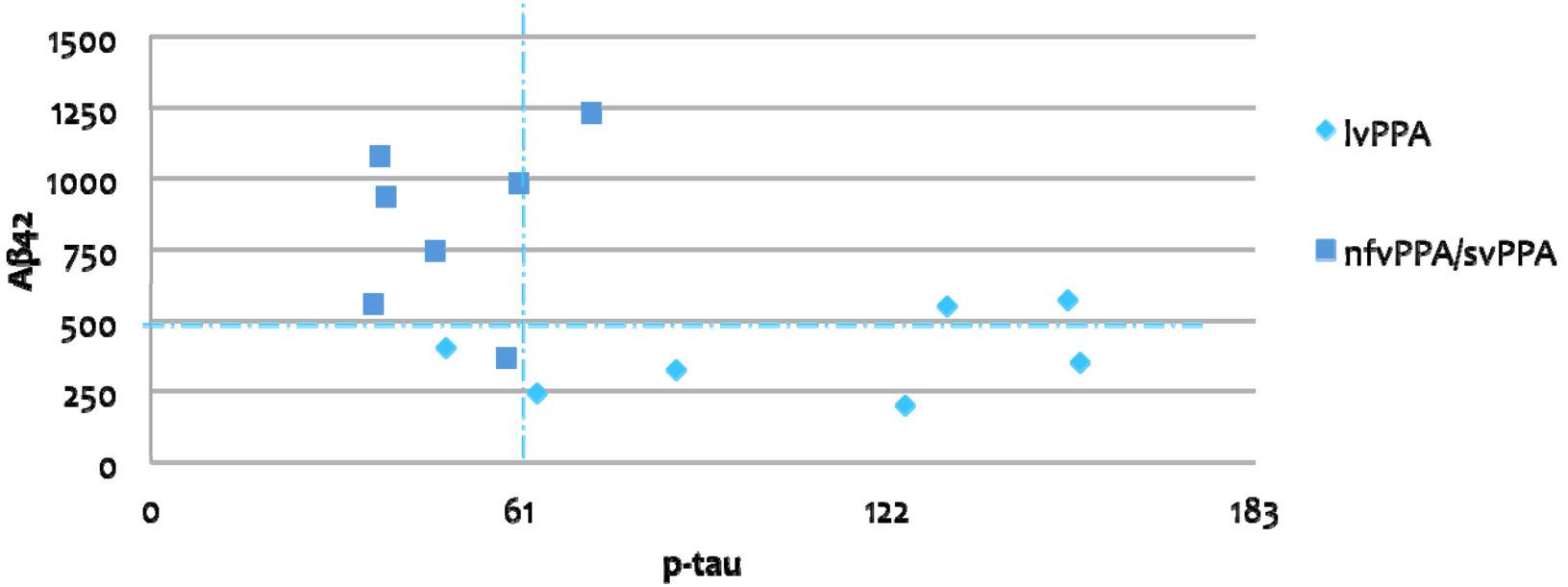
RISULTATI

* ***Confronto con malattia di Alzheimer ad esordio «tipico»***



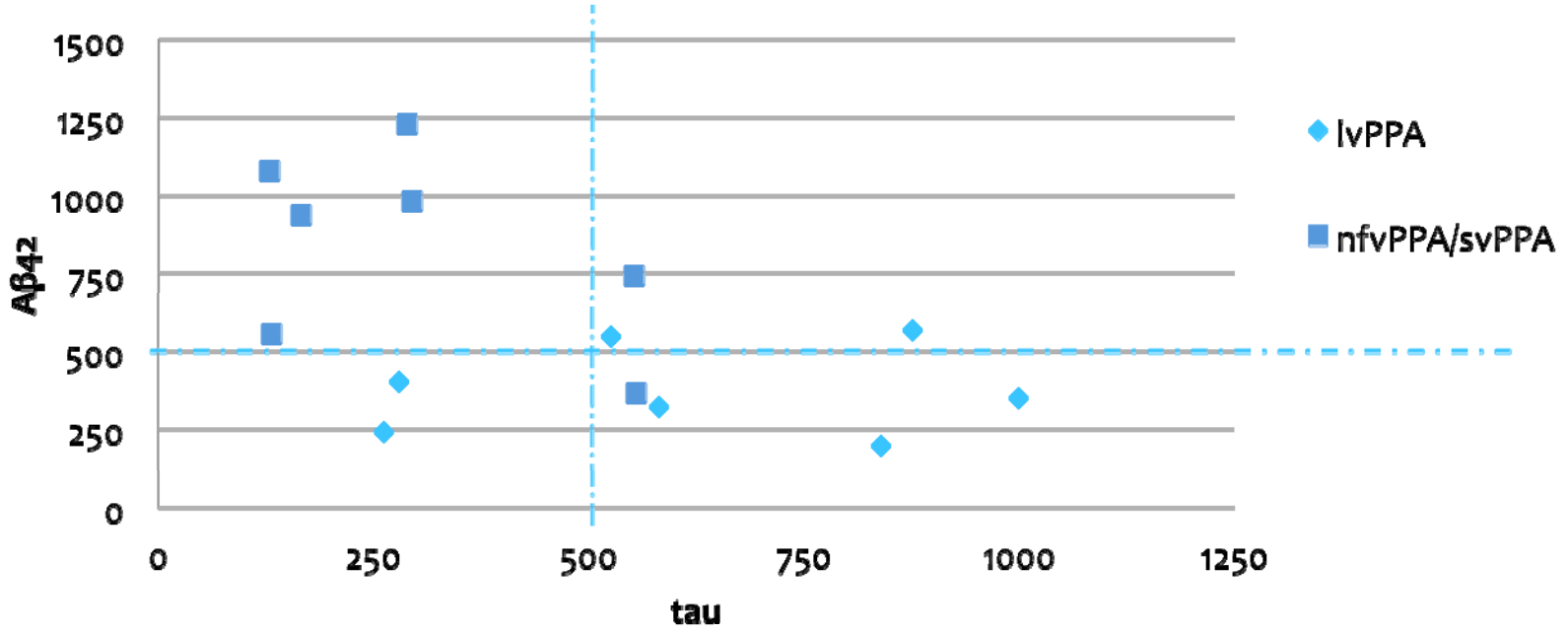
RISULTATI

* ***Pattern liquorali nelle PPA***



RISULTATI

* ***Pattern liquorali nelle PPA***



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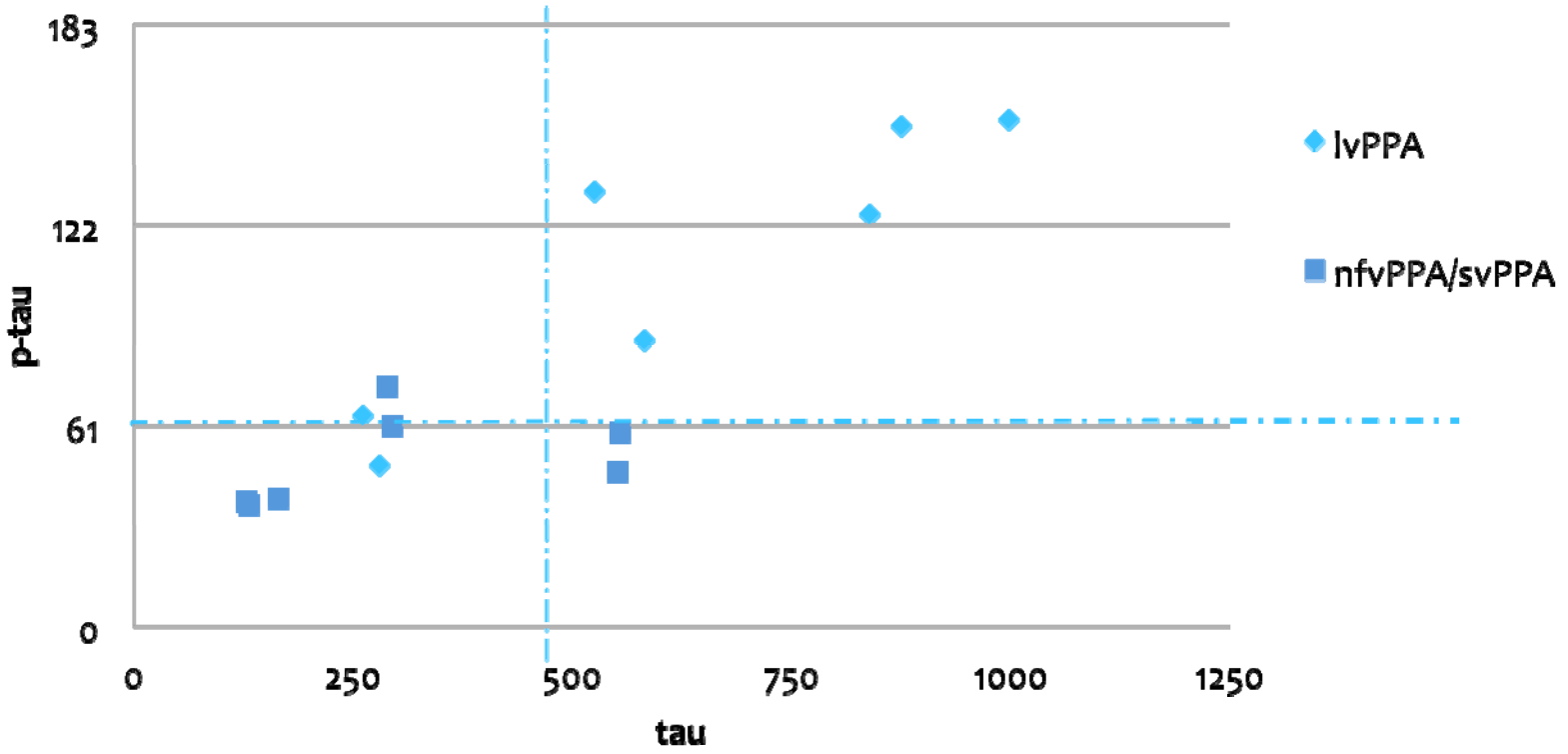
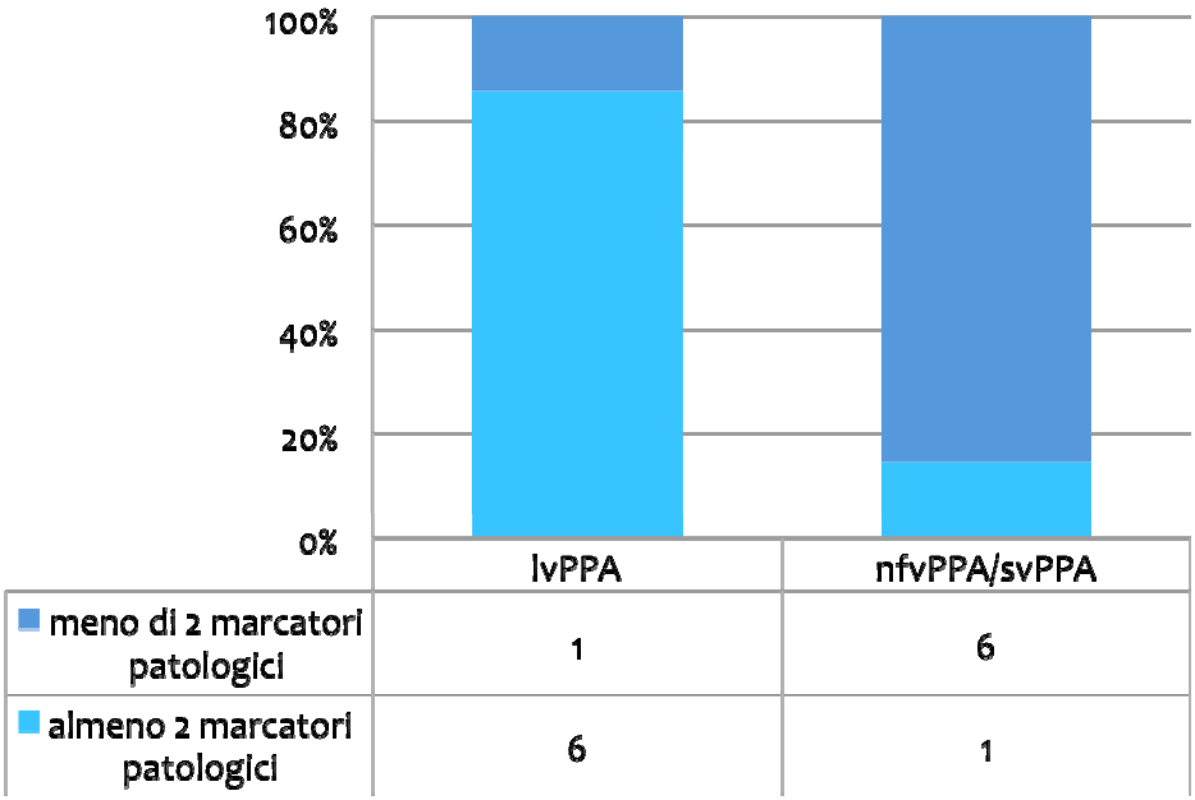


RISULTATI

* ***Pattern liquorali nelle PPA***



Biomarcatore	Valori normativi
Aβ42	>500
Tau	<500
p-Tau	<61

RISULTATI

Le concentrazioni dei biomarcatori liquorali sono differenti nei pazienti con lvPPA e con svPPA/nfvPPA (concentrazione media Aβ42: 377 [±142,5] pg/mL vs 842 [±303,2] pg/mL; concentrazione media tau: 623 [±291,9] pg/mL vs 302 [±184,5] pg/mL; concentrazione media p-tau: 109 [±42,4] pg/mL vs 50,6 [±14] pg/mL. Nei pazienti con lvPPA, inoltre, le concentrazioni medie dei tre biomarcatori sono sovrapponibili alle concentrazioni riscontrate in un campione di 83 pazienti con AD ricoverati presso il nostro reparto dal gennaio 2009 al marzo 2011 (Aβ42: 326 [±166] pg/mL; tau: 649,5 [±370,1] pg/ml; p-tau: 100[±40] pg/mL). Considerando infine come “caratteristico” per AD un pattern liquorale con almeno due marcatori liquorali patologici, risulta che 6/7 pazienti con lvPPA e solo 1/7 nel gruppo svPPA/nfvPPA presentano un profilo liquorale da AD.

CONCLUSIONI

* La PPA era considerata, fino a poco tempo fa, una variante della FTD e, pertanto, priva di qualsiasi possibile strategia terapeutica. La recente scoperta che alcune forme di PPA presentano caratteristiche patogenetiche comuni all'AD ha aperto nuovi orizzonti sia diagnostici sia terapeutici. I nostri dati, pur permanendo la necessità di ampliare la dimensione del campione, dimostrano che i biomarcatori liquorali possono rivelarsi un utile strumento nella diagnosi differenziale delle PPA, offrendo la possibilità, anche nelle fasi più precoci di malattia, di un intervento terapeutico mirato.