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Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology

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ABSTRACT

Although amyloid pathology plays a role in epilepsy, little is known about the relationship between beta amyloid and progression to Alzheimer's disease (AD) among patients with late-onset epilepsy of unknown origin (LOEU). This multicenter, observational, prospective study enrolled 40 consecutive non-demented adults diagnosed with LOEU, together with 43 age- and sex-matched healthy controls. All patients completed neuropsychological tests, core CSF AD biomarkers assessment ($A\beta_{1-42}$, total tau, and phosphorylated tau), and follow-up for a mean of 3 years to verify cognitive decline. Despite age and baseline cognitive performance were similar to healthy controls, patients with LOEU had significant prevalence of CSF pathological $A\beta_{1-42}$ (<500 pg/mL; 37.5%), 7.5% displaying an AD-like CSF pattern. Moreover, 17.5% of patients with LOEU converted to AD dementia, versus none among healthy controls ($p < 0.005$). Patients with LOEU with pathological $A\beta_{1-42}$ had a hazard ratio 3.4 (CI 0.665–17.73) for progression to AD dementia at follow-up. Patients with LOEU have a high prevalence of abnormal CSF $A\beta_{1-42}$ and progression to AD dementia compared with healthy controls, and therefore should be monitored for cognitive decline.

1. Introduction

Epilepsy is a neurological disorder reflecting a transient brain dysfunction due to several different causes (Fisher et al., 2014). The incidence of epilepsy and first unprovoked seizure in adulthood increases with age, especially over age 55 years (Hauser et al., 1993). Among patients with late-onset epilepsy (LOE), more than 20% of cases have unknown etiology (LOE of unknown origin [LOEU]) (Costa et al., 2016; Hauser et al., 1993). Population-based studies highlight overlapping prevalence rates of epilepsy and dementia in the aging population (Hermann et al., 2008). Moreover, epilepsy has been reported with high prevalence among patients with Alzheimer's disease (AD) dementia (Cretin et al., 2016; Sarkis et al., 2017; Vossel et al., 2013). Translational evidences point to a link between amyloid deposition, epilepsy, and cognitive decline (Joutsa et al., 2017; Larner, 2010; Palop and Mucke, 2009). Seizures induce hippocampal morphological alterations and further cognitive decline (Pitkänen et al., 2002; Pitkänen and Sutula, 2002). Accumulation of amyloid plaques, pivotal in the processes leading to AD (Bloom, 2014; Jansen et al., 2015; Lewczuk et al., 2017), has also been found in refractory epilepsy (Sima et al., 2014). In addition, $A\beta_{1-42}$ can elicit epileptiform activity in vivo even before causing neuronal loss (Palop and Mucke, 2009), and epileptic activity itself contributes to cognitive decline in experimental AD models (Palop et al., 2007; Palop and Mucke, 2009). Thus, $A\beta_{1-42}$ has been addressed as 1 of the pathogenic link between epilepsy and cognitive decline.

Although consistent evidence associates amyloid pathology with epilepsy, few studies addressed CSF $A\beta_{1-42}$ in patients with epilepsy (Hermann et al., 2008; Joutsa et al., 2017; Mackenzie and Miller, 1994; Sheng et al., 1994). Brain $A\beta_{1-42}$ accumulation has been reported in patients with childhood onset epilepsy after very-long-term follow-up, predisposing such patients to neurodegenerative disorders (Joutsa et al., 2017). We recently reported, in an experimental model, that $A\beta_{1-42}$ induces epileptic dysfunction before producing neuronal loss, and that CSF $A\beta_{1-42}$ levels are

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decreased in epileptic patients, suggesting a possible pathogenic role of $A\beta_{1-42}$ in LOEU (Costa et al., 2016). To date, however, no study addressed CSF $A\beta_{1-42}$ and cognitive outcomes in patients with LOEU.

In this prospective, multicenter, observational study, we aimed to define CSF $A\beta_{1-42}$ and cognitive status evolution of individuals with LOEU. We investigated CSF $A\beta_{1-42}$ and core AD core biomarkers in patients with LOEU, correlating it to neuropsychological assessment at the time of epilepsy diagnosis and at follow-up. The results of this study might help clinicians in defining beta amyloid pathology and risk of evolution to AD among patients with LOEU.

2. Methods

2.1. Population

A consecutive series of nondemented patients aged >55 years referring for epilepsy to the Clinics of Neurology of the University of Perugia and the University of Rome "Tor Vergata" (Italy) between 2008 and 2014 was included in the study (Costa et al., 2016). Electroencephalogram (EEG), epilepsy diagnosis, and seizure pattern was characterized according to International League Against Epilepsy Classification criteria, excluding patients with provoked seizures (Beghi et al., 2010; Falco-Walter et al., 2018; Fisher et al., 2014). All patients underwent the same brain MRI protocol, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery, T2*-fast field echo, proton density sequences, and MRA. The medial temporal lobe was visually rated by 2 independent raters who were experts in neuroradiology, blinded to patient status (Liguori et al., 2016; Scheltens et al., 1992). Nondemented patients receiving a diagnosis of LOEU underwent a standardized screening, with medical history, neuropsychological testing (including Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Clinical Dementia Rating scale (CDR) (Morris, 1993), and a complete neuropsychological assessment exploring memory, executive function, attention, language, and visuospatial skills). MMSE, Rey Auditory Verbal Learning Test, and Trail Making Test were performed in all patients; the remaining neuropsychological battery varied according to the need of exploring specific cognitive function. EEG and lumbar puncture were used to measure CSF biomarkers. CDR was completed blinded to patient group, and final score was assigned after group consensus; MMSE score was chosen as the main test score to detect cognitive decline over time. Inclusion criteria for the present study were (1) MMSE score >24 at the baseline and no subjective cognitive complaint; (2) diagnosis of LOEU according to aforementioned guidelines; (3) seizure control, with seizure control being defined as no seizure at all or ≥50% reduction in baseline seizure frequency with antiepileptic drugs (AEDs) (Bedetti et al., 2017), to avoid seizure-induced beta amyloid variations (Joutsa et al., 2017); (4) availability of a 20-minute resting-state EEG at the baseline. All patients received AED with optimal compliance. Exclusion criteria were (1) a medical history of other significant neurological or psychiatric disorders; (2) diagnosis of dementia, MMSE score <24 or use of acetylcholinesterase inhibitors; (3) use of antipsychotic drugs or lithium. Primary endpoint was progression to dementia of any type and AD dementia at follow-up. For such purpose, MMSE score and CDR were used to monitor cognitive decline. Secondary endpoint was MMSE score reduction at follow-up. All demographic and clinical factors were taken into account to assess possible predictor of conversion to dementia. Dementia and dementia due to AD were diagnosed according to National Institute on Aging-Alzheimer's criteria (McKhann et al., 2011), taking into account personal anamnesis, clinical course, cognitive assessment, and CSF findings (McKhann et al., 2011). As a control group for CSF biomarkers and cognitive status, we recruited 43 cognitively normal (CDR 0 and MMSE score >24) age- and sex-matched nonepileptic subjects undergoing lumbar puncture as a diagnostic procedure for differential diagnosis of headache disorders or infectious CNS disease with normal results. All subjects gave written informed consent for lumbar puncture, CSF collection and examination, neuropsychological assessment, and the use of these data for research purposes. Protocol was approved by our Internal Advisory Board. All diagnoses were made in a multidisciplinary consensus meeting according to specific diagnostic criteria for dementia and dementia due to AD (McKhann et al., 2011).

2.2. EEG

Video EEG recordings were obtained using a 21-electrodes standard international 10-20 electrode placement (Gouw et al., 2017). Recordings took place during routine 20-minute sessions. Patients were seated in a reclined bed in a fully lit room, with sound attenuation. EEG technicians and physicians supervising EEG recording monitored it carefully, alerting the patients by sound stimuli at first signs of drowsiness. All investigators and technicians were blinded for epilepsy diagnosis, neuropsychological assessment results, and cognitive status.

2.3. CSF biomarkers

CSF samples were collected by lumbar puncture between the L3/L4 and L4/L5 intervertebral space and analyzed at the University Hospital of Perugia—Neurochemistry Laboratory. Lumbar puncture was performed within 2 months after epilepsy diagnosis, and at least 3 weeks after the last seizure. All analyses were performed in a blinded fashion. CSF analysis included routine chemical physical parameter (glucose, total proteins, albumin, and cell count) and measurement of classical biomarkers of AD ($A\beta_{1-42}$, total tau [t-tau], and phosphorylated tau [p-tau]) by means of enzyme-linked immunosorbent assay kits (Fujirebio). $A\beta_{1-42}$ was defined pathologic when <500 pg/mL; AD-like CSF was defined as pathologic results of $A\beta_{1-42}$ (<500 pg/mL), with pathologic tau (>400 pg/mL) or p-tau (>60 pg/mL) (Albert et al., 2011; Lewczuk et al., 2015).

2.4. Data analysis

Statistical analysis was performed using R software 3.1 (R Core Team, 2017). Continuous variables were described by means and standard deviations, whereas categorical ones were summarized with counts and percentages. Rates of AD-like CSF pattern and Aβ positivity were reported along with their Wilson 95% confidence intervals. Normality of continuous variables was checked with Shapiro-Wilk's test. Differences of continuous variables were tested with Student's t-test or Mann-Whitney *U* test wherever appropriate. Differences of categorical variables were tested with χ^2 test or Fisher's exact test wherever appropriate. Predictors of time to conversion to AD or any dementia were assessed using univariate and multivariate Cox proportional hazards regression models. In the absence of a conversion event, data were censored at the most recent follow-up visits. Demographic and clinical covariates that were associated with earlier conversions on univariate analysis were then included in the multivariate analysis. Hazard proportionality was assessed through analysis of scaled Schoenfeld residuals. Significance level of 5% was assumed for all the analyses.

3. Results

Overall, 54 consecutive patients accepted to undergo neuropsychological assessment and lumbar puncture and were enrolled.

Neuropsychological testing was performed at the baseline (at LOEU diagnosis). Fourteen of 54 patients undergoing neuropsychological testing resulted having MMSE score <24 and/or CDR >0 and were thus excluded according to specified enrollment criteria. No significant differences in demographic data were detected between excluded and included patients.

Forty patients with LOEU were enrolled with slight female prevalence (n = 23, 57.5%), and 43 healthy age- and sex-matched controls (Table 1). Mean age was 70.0 ± 6.4 years in LOEU group, similar to controls (67.5 ± 5.5). Family history of dementia was reported in 3 patients in LOEU group and 3 healthy controls; no history of head trauma in the previous 10 years was reported. EEG and clinical history revealed prevalence of focal (85.0%) seizures, more frequently with a temporal origin (35.0%). None of our patients had status epilepticus. Baseline EEG was normal in 20.0% of the patients. Slow activity without epileptic graphoelements was found in 32.5% of the cohort, whereas epileptiform activity was detected in 47.5% of cases. All patients received AED treatment. During follow-up, no major cardiovascular event occurred.

Patients with LOEU and healthy controls had similar cognitive performances, but prevalence of abnormal CSF AD biomarkers was higher in LOEU group. Mean LOEU MMSE score at the baseline was 26.9 ± 1.9 (25–30). After informed consent, all 40 enrolled patients underwent lumbar puncture at the baseline. Mean $A\beta_{1\text{-}42}$ was 703.9 pg/mL, and mean t-tau and p-tau were 300.9 and 63.0 pg/mL, respectively (Table 1). $A\beta_{1\text{-}42}$ and t-tau were, respectively, lower and higher among patients with LOEU compared with healthy controls ($p < 0.05$). Among patients with LOEU, 15 were found to have pathological $A\beta_{1\text{-}42}$ (37.5%; 95% CI = 24.2%–53.0%), whereas only 1 was detected among healthy controls ($p < 0.05$). An AD-like CSF pattern was detected in 3 of 40 patients with LOEU (7.5%). Moreover, among patients with normal beta amyloid, pathological p-tau was more frequent among LOEU compared with controls ($p < 0.05$) (Table 1).

Comparing patients with normal ($A\beta_{1\text{-}42}-$, n = 25, 62.5%) and pathological $A\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}+$, n = 15, 37.5%), no differences were found regarding demographic characteristic such as age and gender (Table 2). Frontal and temporal epilepsy, as well as normal EEG, were more frequent among patients with normal $A\beta_{1\text{-}42}$. The 2 groups had similar mean MMSE score at the baseline (26.9 ± 1.9 vs. 27.6 ± 1.3, $p = 0.900$) and follow-up duration, with a mean of 3 years (3.1 vs. 3.2 years, $p = 0.802$). Compared with $A\beta_{1\text{-}42}-$ LOEU patients, $A\beta_{1\text{-}42}+$ patients had a higher rate of conversion to dementia (46.2% vs. 17.4%, p=0.119) and conversion to AD dementia (33.3% vs 8.0%, $p = 0.081$) (Table 2).

Table 1
Demographic, clinical, and biochemical characteristics of the population

	Patients with LOEU	Healthy controls	*p*-value
N	40	43	
Male (%)	17 (42.5%)	20 (46.5%)	ns
Age, mean ± SD (range), years	70.0 ± 6.4 (57-84)	67.5 ± 5.5 (59-78)	ns
Epilepsy			
Focal—Unknown focus (%)	18 (45.0%)	-	
Focal—Frontal focus (%)	3 (7.5%)	-	
Focal—Temporal focus (%)	14 (35.0%)	-	
Generalized (%)	5 (12.5%)	-	
EEG			
Epileptic (%)	19 (47.5%)	-	
Normal (%)	8 (20.0%)	-	
Slow (%)	13 (32.5%)	-	
MMSE score, mean ± SD	26.9 ± 1.9	27.6 ± 1.3	ns
Other cognitive testing (mean ± SD)			
RAVLT-immediate	36.15 ± 10.02	39.74 ± 8.56	ns
RAVLT-delayed	7.33 ± 1.89	8.02 ± 1.96	ns
TMT-A	56.83 ± 29.68	46.74 ± 23.32	ns
TMT-B	160.97 ± 57.28	139.79 ± 49.32	ns
CSF biomarkers			
$A\beta_{1\text{-}42}$ (pg/mL)	703.9 ± 388.3 (23-1711)	975 ± 275 (452-1620)	<0.001
t-tau (pg/mL)	300.9 ± 213.3 (80-1200)	219.2 ± 77.4 (99-498)	<0.05
p-tau (pg/mL)	63.0 ± 78.9 (12-452)	42 ± 11 (21-67)	ns
$A\beta_{1\text{-}42}$ positive (<500 pg/mL) [mean (pg/mL) ± SD]	15 (37.5%) [334.6 ± 118.5]	1 (2.3%)	<0.05
Normal $A\beta_{1\text{-}42}$ and abnormal p-tau/t-tau [p-tau mean (pg/mL) ± SD]	4 (10%) [82.0 ± 24.2]	1 (2.3%)	0.82
AD-like CSF pattern (yes)	3 (7.5%)	0	<0.05
Conversion to dementia			
Any dementia (%)	10 (25%)	0	<0.005
AD dementia (%)	7 (17.5%)	0	
Nonconversion (%)	30 (75%)	0	
AED regimen			
Monotherapy (%)	34 (85.0%)	-	
Polytherapy (%)	6 (15.0%)	-	
AED prescription			
Levetiracetam (%)	12 (30.0%)	-	
Levetiracetam + Other (%)	2 (5.0%)	-	
Valproate (%)	5 (12.5%)	-	
Valproate + Other (%)	2 (5.0%)	-	
Carbamazepine (%)	4 (10.0%)	-	
Lamotrigine (%)	4 (10.0%)	-	
Oxcarbazepine (%)	2 (5.0%)	-	
Phenobarbital (%)	3 (7.5%)	-	
Topiramate (%)	1 (2.5%)	-	
Topiramate + Other (%)	2 (5.0)	-	

LOEU, late-onset epilepsy of unknown origin; AD, Alzheimer's disease; AED, antiepileptic drug; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test.

Table 2
Comparison of demographic and clinical data between patients with normal $A\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}-$) and pathological $A\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}+$) patient subgroups

	$A\beta_{1\text{-}42}-$	$A\beta_{1\text{-}42}+$	*p*-value
N (%)	25 (62.5%)	15 (37.5%)	
Gender (male %)	10 (40.0%)	7 (46.7%)	ns
Age, mean ± SD (range), years	68.5 ± 6.0 (57.0–79.0)	72.5 ± 7.1 (59.0–84.0)	ns
Epilepsy			
Focal—Unknown focus (%)	7 (28.0%)	11 (73.3%)	0.020
Focal—Frontal focus (%)	3 (12.0%)	0 (0.0%)	
Focal—Temporal focus (%)	12 (42.9%)	2 (13.3%)	
Generalized (%)	3 (12.0%)	2 (13.3%)	
EEG			
Epileptic (%)	12 (48.0%)	7 (46.7%)	ns
Normal (%)	6 (24.0%)	2 (13.3%)	
Slow (%)	7 (28.0%)	6 (40.0%)	
MMSE score at the baseline, mean ± SD	26.7 ± 1.9	26.8 ± 1.9	ns
Other cognitive testing (mean ± SD)			
RAVLT-immediate	38.0 ± 8.92	32.07 ± 10.71	ns
RAVLT-delayed	7.56 ± 1.94	6.93 ± 1.79	ns
TMT-A	49.88 ± 24.78	68.4 ± 34.23	ns
TMT-B	147.08 ± 50.22	184.13 ± 62.42	ns
Follow-up, mean ± SD, years	3.1 ± 2.1	3.2 ± 1.3	ns
MMSE score lost per year, mean ± SD	1.1 ± 2.5 (−1.1–11.1)	1.6 ± 1.5 (0–5.0)	ns
Conversion to dementia			
Any dementia (%)	4 (17.4%)	6 (46.2%)	ns
AD dementia (%)	2 (8.0%)	5 (33.3%)	ns
Nonconversion (%)	21 (82.6%)	9 (53.8%)	ns

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test.

Demographic, clinical, and biochemical factors were investigated via Cox regression models to assess prediction of conversion to AD (Table 3). No conversion to AD dementia was observed beyond 3.5 years of follow-up (Fig. 1). Demographic factors, epileptiform activity during the baseline EEG, AEDs prescription, and AEDs regimen did not influence progression to AD dementia. On the contrary, CSF biomarkers were strictly associated with conversion to dementia at the last follow-up (Table 3). In particular, considered as a continuous variable, CSF $A\beta_{1\text{-}42}$ levels inversely correlated with conversion to AD dementia (hazard ratio [HR] 0.996, $p = 0.019$). t-tau and p-tau positively influenced the progression to AD ($p < 0.01$). CSF biomarkers role was further supported by the influence of $A\beta_{1\text{-}42}$/p-tau and $A\beta_{1\text{-}42}$/t-tau ratios on progression to dementia (HR 0.049 and 0.735, respectively, $p < 0.01$). Being in the pathological $A\beta_{1\text{-}42}$ group (<500 pg/mL), even though not reaching statistical significance, conveyed to patients with LOEU an HR of 3.4 in progression to AD dementia at follow-up (Table 3). Similar to AD dementia, Cox regression models confirmed the findings also for progression to any dementia (Table 3). No combination of clinical and biochemical features was found to predict AD through multivariate Cox regression.

Nevertheless, a significant proportion of patients with LOEU with pathological $A\beta_{1\text{-}42}$ did not convert to dementia at the follow-up (Table 2). In particular, among patients with LOEU with pathological $A\beta_{1\text{-}42}$ (n = 15), 9 (53.8%) had stable cognitive performances after a 3-year follow-up, without converting to any dementia, 1 converted to non-AD vascular dementia, diagnosed according to NINDS criteria (Perneczky et al., 2016; Roman et al., 1993), and 1 converted to frontotemporal dementia (Rascovsky et al., 2011). No differences regarding demographic, baseline clinical and MMSE score, or follow-up duration were detected among converter depending on CSF $A\beta_{1\text{-}42}$ status. Higher MMSE score loss per year was detected among $A\beta_{1\text{-}42}+$ patient subgroup (Table 4).

4. Discussion

LOEU origin represents more than 20% of all LOEs (Hauser et al., 1993). Even though several animal studies have associated amyloid pathology with epilepsy, few evidences are available regarding $A\beta_{1\text{-}42}$ CSF levels in patients with epilepsy (Hermann et al., 2008; Joutsa et al., 2017; Mackenzie and Miller, 1994; Sheng et al., 1994). Because $A\beta_{1\text{-}42}$ has epileptogenic properties, and drives neurodegeneration, beta amyloid represents a matter of concern among patients with LOEU, as it might be addressed as a common pathway of 2 different but intertwined processes (Costa et al., 2016). To our knowledge,

Table 3
Role of clinical and biochemical characteristics on progression to AD dementia and dementia of any type according to Cox regression model

	Progression to AD dementia		Progression to any dementia	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender (male)	0.810 (0.181–3.629)	ns	1.273 (0.340–4.764)	ns
Age (years)	1.066 (0.953–13.192)	ns	1.080 (0.981–1.189)	ns
EEG	1.222 (0.272–5.489)	ns	1.222 (0.272–5.489)	ns
Levetiracetam	1.652 (0.368–7.418)	ns	0.805 (0.200–3.238)	ns
Polytherapy	1.054 (0.126–8.788)	ns	0.903 (0.111–7.362)	ns
$A\beta_{1\text{-}42}$ (pg/mL)	0.996 (0.992–0.999)	0.019	0.998 (0.995–1.000)	0.040
t-tau (pg/mL)	1.005 (1.002–1.008)	0.002	1.004 (1.002–1.007)	0.002
p-tau (pg/mL)	1.005 (1.001–1.010)	0.003	1.005 (1.001–1.009)	0.025
$A\beta_{1\text{-}42}$/t-tau ratio	0.049 (0.006–0.364)	0.003	0.049 (0.006–0.364)	0.003
$A\beta_{1\text{-}42}$/p-tau ratio	0.735 (0.601–0.898)	0.003	0.843 (0.741–0.961)	0.010
$A\beta_{1\text{-}42}+$	3.433 (0.665–17.73)	0.140	2.264 (0.635–8.076)	0.210

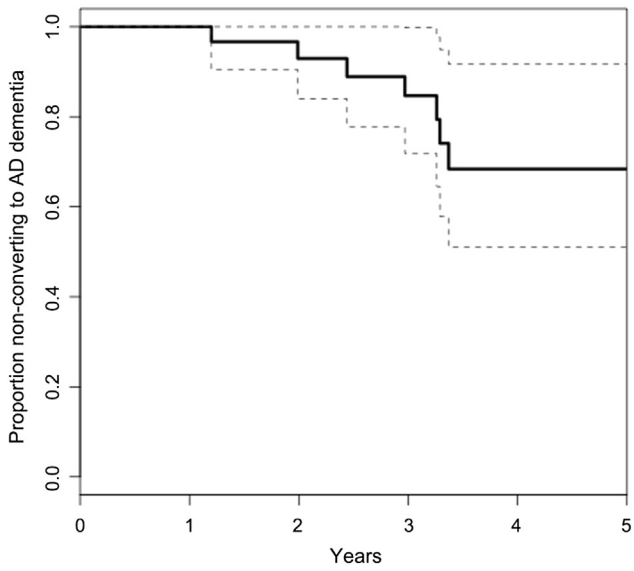

Fig. 1. Kaplan-Maier estimate of survival curve for the risk of AD dementia.

this is the first study to address CSF beta amyloid and its correlation with cognitive status changes among patients with LOEU.

Regarding CSF biomarkers, we found a critical prevalence of pathological $A\beta_{1\text{-}42}$ among LOEU population compared with healthy controls, even after adjusting for age, gender, and MMSE score. The fact that reduced CSF beta amyloid can be detected among seizure-free LOEU might suggest that $A\beta_{1\text{-}42}$ levels are related to epileptogenic processes rather than to seizure frequency, as already suggested by Joutsa et al for patients with childhood onset epilepsy (Joutsa et al., 2017). However, given that 17.5% (7/40) of nondemented patients with LOEU evolved within 3 years to AD-type dementia, one may argue whether the abnormalities of CSF beta amyloid that we detected have been the clue to a very early phase in AD process. If this is the case, then the proportion of patients with LOEU converting to AD has been eventually underestimated by our study, and, even though requiring longer follow-up, it is a matter of serious concern. If, otherwise, such patients have mild cognitive impairment, and not prodromal AD, longer follow-up might highlight an even higher risk of cognitive decline. Thus, because evolution to AD dementia was driven by pathological CSF biomarkers, we strongly suggest to assess cognitive status and CSF biomarkers in patients with LOEU. Such screening is mandatory to allow very early AD diagnosis among patients with LOEU, allowing access to novel treatment (Sevigny et al., 2016).

Nevertheless, because survival analysis showed poor progression to AD beyond 3 years from LOEU diagnosis, the beta amyloid status in patients with stable cognitive performances represents a challenging issue to deal with. In our study, 53.8% of patients with LOEU and pathologic $A\beta_{1\text{-}42}$ (<500 pg/mL) had normal cognition at the baseline as well as after 3 years of follow-up. Because demographic and clinical data, EEG, and CSF biomarkers did not differ from the other half of the subgroup, among these patients beta amyloid pathology may strictly represent a proepileptogenic factor, without implying cognitive decline, at least for a very early stage. The proepileptogenic effects of $A\beta_{1\text{-}42}$, already identified in preclinical models before neurodegeneration (Costa et al., 2016), might find its clinical correlate in the results of the present study. Thus, given that the diagnosis of LOEU stands on the basis of unknown factors, we might suppose that beta amyloid, in these patients, is the critical factor to develop epilepsy, supporting the hypothesis of an Aβ-mediated epilepsy. On the other side, because amyloid pathology is common in cognitively normal elderly patients, longer follow-up will help in defining the role of CSF biomarkers alterations among the patients with LOEU.

Summing up, the results of this study highlight that pathological $A\beta_{1\text{-}42}$ levels are very common among patients with LOEU at the time of epilepsy diagnosis and that CSF beta amyloid status drives conversion to dementia after a 3-year follow-up. Thus, a standard cognitive status examination is needed in patients with LOEU to avoid late AD diagnosis. Moreover, patients with LOEU might represent a population to consider in trials addressing preclinical stages and conversion to AD dementia. Nevertheless, even though a high rate of patients with LOEU and pathological beta amyloid tends to evolve to AD dementia, half of these patients have stable cognitive performances even after years. In this specific subgroup, undistinguishable for demographic, clinical, and cognitive characteristics at the baseline from their pairs, $A\beta_{1\text{-}42}$ might trigger and participate to epileptogenesis without leading to cognitive decline. Hence, the unknown origin in some of these patients might be indeed tracked down to the processes

Table 4
Comparison of demographic and clinical data between patients that progressed to dementia and that did not within the $A\beta_{1\text{-}42}$ + patient subgroup

	Nonconversion to AD dementia	Conversion to AD dementia	*p*-value
N	10[a]	5	
Gender (male %)	4 (40.0%)	3 (60.0%)	ns
Age, mean ± SD (range), years	71.3 ± 8.1 (59.0–84.0)	75.0 ± 4.3 (70.0–79.0)	ns
Epilepsy			
Focal—Unknown focus (%)	6 (60.0%)	5 (100.0%)	ns
Focal—Frontal focus (%)	0 (0.0%)	0 (0.0%)	
Focal—Temporal focus (%)	2 (20.0%)	0 (0.0%)	
Generalized (%)	2 (20.0%)	0 (0.0%)	
EEG			
Epileptic (%)	5 (50.0%)	2 (40.0%)	ns
Normal (%)	2 (20.0%)	0 (0.0%)	
Slow (%)	3 (30.0%)	3 (60.0%)	
t-tau (pg/mL)	245.1 ± 67.5	514.0 ± 418.7	ns
p-tau (pg/mL)	39.4 ± 12.2	185.0 ± 190.1	ns
MMSE score at the baseline, mean ± SD	26.8 ± 2.1	26.8 ± 2.1	ns
Follow-up, mean ± SD, years	3.6 ± 1.5	2.5 ± 1.0	ns
MMSE lost per year, mean ± SD	0.7 ± 0.6	3.1 ± 1.3	0.004

MMSE, Mini-Mental State Examination.
[a] Nine patients with normal cognitive function, 1 patient with vascular cognitive impairment.

due to pathological beta amyloid, suggesting an Aβ-mediated epilepsy.

4.1. Limitations

There are some limitations in the present study. First, the small sample derived from consecutive enrollment of adults with LOEU in 3 different tertiary centers for epilepsy; thus, the population selected might not completely represent the general adult population with LOEU. However, we focused on a very specific epilepsy subtype, with homogeneous diagnosis and accurate prospective data collection, which strengthens the value of the sample. Of note is the low prevalence rate of amyloid positivity in our control group, which could be entirely attributed to sampling variability due to the consecutive enrollment of the patients. Second, although neuropsychological assessment was based on broad test battery exploring all cognitive domains, MMSE score and CDR were chosen as benchmarking test to monitor cognitive decline over time to avoid dispersion among several neuropsychological testing. Third, mean follow-up was 3 years, which might lead to wonder if CSF abnormalities detected in adults with LOEU are the hallmark of a very prodromal phase of AD, and if all patients with LOEU will progress to AD with longer follow-up. However, in a population aged 70 years at the baseline, we found no progression to AD beyond 3.5 years. Moreover, if this is the case, then our study underestimating the risk of dementia among adults with LOEU, thus further confirming the need to monitor cognitive function.

5. Conclusion

LOEU was significantly associated with CSF beta amyloid alterations and progression to AD dementia; thus, patients with LOEU should be monitored for cognitive decline to avoid late diagnosis. Moreover, pathologic CSF $A\beta_{1-42}$ findings among patients with LOEU and stable cognitive performance suggest that $A\beta_{1-42}$ might also primarily mediate epileptogenesis.

Disclosure statement

The authors report no conflict of interest.

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