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Clinical short communication

Factors underlying the development of chronic temporal lobe epilepsy in autoimmune encephalitis

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ABSTRACT

Purpose: Limbic encephalitis (LE) is an autoimmune condition characterized by amnestic syndrome, psychiatric features and seizures. Early diagnosis and prompt treatment are crucial to avoid long-term sequelae, including psycho-cognitive deficits and persisting seizures.

The aim of our study was to analyze the characteristics of 33 LE patients in order to identify possible prognostic factors associated with the development of chronic epilepsy.

Methods: This is a retrospective cohort study including adult patients diagnosed with LE in the period 2010–2017 and followed up for ≥12 months. Demographics, seizure semiology, EEG pattern, MRI features, CSF/serum findings were reviewed.

Results: All 33 LE patients (19 M/14F, mean age 61.2 years) presented seizures. Thirty subjects had memory deficits; 22 presented behavioural/mood disorders. Serum and/or CSF auto-antibodies were detected in 12 patients. In 31 subjects brain MRI at onset showed typical alterations involving temporal lobes. All patients received immunotherapy. At follow-up, 13/33 had developed chronic epilepsy; predisposing factors included delay in diagnosis ($p = .009$), low seizure frequency at onset ($p = .02$), absence of amnestic syndrome ($p = .02$) and absence/rarity of inter-ictal epileptic discharges on EEG ($p = .06$).

Conclusions: LE with paucisymptomatic electro-clinical presentation seemed to be associated to chronic epilepsy more than LE presenting with definite and severe "limbic syndrome".

1. Introduction

In recent years novel autoantibody-related neurological disorders have been recognized and studied with growing interest [1–5]. Early identification of clinical features, reliable methods of diagnosis, and prompt immunotherapy can lead to a favorable outcome in such acute/subacute neurological conditions, which may be associated with significant morbidity and mortality if left untreated [6,7]. In this context, autoimmune limbic encephalitis (LE), a rare and potentially treatable condition, is, unfortunately, often misdiagnosed [8–11]. Although it was commonly considered of paraneoplastic origin [3,12,13], the recent identification of antibodies (Abs) directed against neuronal surface antigens (NSAbs) contributed to reveal that a substantial proportion of cases LE is not associated with any malignancy [7,14]. Different Abs targeting extracellular epitopes of cell surface receptors and trans-synaptic protein complexes are recognized to be responsible for specific encephalitis subtypes [14–16].

LE is typically characterized by subacute amnestic syndrome, usually evolving over weeks to months, focal seizures and psychiatric features. Epileptic seizures, whose semiology generally suggests the involvement of temporo-mesial structures, are commonly considered as a cardinal symptom at disease onset. The immune-mediated mechanisms underlying epileptic phenomena in LE could not only induce ictogenesis during the acute phase of the disease, but also contribute to the long-standing epileptogenic process that leads to the development of chronic epilepsy. Seizures usually show a good response to immunotherapy even though, in a proportion of cases, they can persist over time [7,10,14,17]. In this scenario, seizure recurrence might be

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either the expression of an enduring inflammatory insult, poorly responsive to therapy, or, alternatively, the manifestation of a chronic epileptic disorder. Factors predisposing to the development of chronic epilepsy have not been fully identified, given the complexity of LE pathogenesis and its phenotypical spectrum [14,18–23].

The aim of this retrospective study, including a series of 33 consecutive LE patients, was to define the factors predisposing to the development of chronic focal epilepsy through the analysis of electro-clinical, laboratory and neuroimaging findings.

2. Patients and methods

Our retrospective study included a cohort of 33 consecutive adult patients, referred to the Department of Neurosciences and Mental Health ("Sapienza" University of Rome, Italy) and to the Epilepsy Unit of IRCCS Neuromed (IS, Italy), and diagnosed with LE between January 2011 and January 2017. In all included subjects the diagnosis of LE met the recently proposed diagnostic criteria [10]. Demographics, clinical manifestations, seizure semiology, ictal/interictal electroencephalography (EEG), MRI features, complete cerebrospinal fluid (CSF) and serum findings, additional procedures (i.e. diagnostic tests for malignancies, including chest and abdomen-pelvis CT, gynecological/urologic/dermatological examinations, mammography/breast ultrasound, and thyroid/testicle/prostate ultrasonography; in selected cases endoscopic procedures for gastro-intestinal malignancies) and clinical outcome, were systematically collected and reviewed. We also carefully verified that in all selected patients etiologies other than autoimmune disorders had been reasonably excluded through adequate tests. Clinical features at LE onset, including seizure type and frequency, memory disorders and mood/behavioral changes, along with treatments (including anti-epileptic drugs (AEDs), immunotherapy and psychiatric medications) were considered for analysis. The same variables were examined during follow-up to document changes in seizure frequency, cognitive performances and mood/behavioral functioning. Brain 1.5 or 3 T MRI and prolonged video-EEG monitorings were available for revision in all patients (in particular, recorded seizures and interictal epileptiform discharges – IED - were quantitatively assessed). The assessment of cognitive and behavioral disturbances was performed through Minimental state examination test (MMSE), montreal cognitive assessment (MOCA), Addenbrooke's Cognitive examination (ACE), Hamilton Depression Rating Scale (HDRS) and modified Rankin Scale (mRS); all these tests, selected according to patients' clinical conditions, were performed at first observation and then periodically (in most cases at 1, 3, 6, 12 months, then annually).

As regards laboratory tests, NSAbs and Abs targeting intracellular antigens were assessed on serum and CSF in all cases (the patients' samples were analyzed in three different laboratories – Clinical Pathology Department of Sapienza University, Neuromed Institute and Clinical Pathology Department of Treviso Hospital; in most cases for the detection of synaptic and intracellular Abs, cell-based immunoassay and immunoblotting were used, respectively).

Complete demographic and clinical data are summarized in Table 1.

2.1. Statistical analysis

First, a descriptive analysis was performed to calculate relative frequencies and means and standard deviations, as appropriate, of all variables of interest. We performed a comprehensive outcome analysis in order to identify all outcome predictors in our patient population. Chi squared test or Fisher's exact test were used as appropriate to test if seizure outcome differed between patients grouped according to the following variables (obtained by the previous selection): sex, age, age at disease onset, seizures frequency at onset, presence of memory and psychiatric dysfunctions, presence of IED, MRI features, time at diagnosis/therapy and duration of follow-up. Statistical analyses were carried out using SPSS for Mac, version 20.0 (IBM Corporation, Armonk, NY, USA). Results were considered significant at $p < .05$.

3. Results

3.1. General clinical data, neuroimaging and laboratory findings

A total of 33 patients (19 males 57.6%, mean age 61.2 years (SD = 15.3 range 18–82) were included in the study. Mean follow-up was 19 months (SD = 11.7, range 12–60 months).

With regard to relevant data in past medical history, 8 (24.2%) individuals reported recent infections and 6 (18.2%) had a history of previous neoplasms. None of the subjects included in the present study reported past or recent history of head trauma or brain injury.

Clinical manifestations at the onset included seizures associated with memory deficits (91%), psychiatric disorders (66.7%) and sleep alterations (30.3%). Memory deficits at first observation (30 subjects) mainly consisted in short-term memory loss and/or attention deficit (MMSE score ranged from 15 to 30; mean score: 23/30). Psychiatric disorders (documented in 22 subjects) were characterized by behavioural changes or mood disturbances, including depression and anxiety, irritability, aggressive behaviour, recurrent episodes of psychomotor agitation. Sleep alterations (10 subjects) consisted in insomnia or REM behaviour disorders.

In 31 (94%) patients brain MRI at onset showed alterations involving mesial temporal lobes: they were bilateral in 22 out of 31 (71%), and in twelve cases they evolved to atrophy at 6–12-month follow-up. Hyponatremia (< 135 mmol/L) was documented in 7 (21,2%) patients. Abs were detected in serum/CSF of 12 (36,3%) subjects: specifically, 7 had Abs anti-VGKC (LGI-1 in 3, CASPR-2 in 4), 2 showed Abs anti-NMDAR, whereas Abs anti-SOX-1, Ri/Hu and GAD65 were detected in one subject each.

3.2. Epileptological data and electro-clinical findings

Focal seizures represented the main clinical presentation of LE in all patients: focal impaired awareness seizures in 23 (69.7%) cases and focal aware seizures in 10 (30.3%); secondary generalized seizures were reported in 12 cases (36.3%), FBDS in 2 subjects (6%). Seizures were recorded during video-EEG monitoring in 16 (48.5%) cases: left temporal lobe onset was detected in 5 seizures, right in 1 and bilateral temporal or bi-hemispheric in 10. IEDs were detected at first available EEG in 21 cases (63.6%). Detailed seizure semiology, interictal and ictal EEG findings are shown in Table 2.

3.3. Therapeutic approach and seizure/epilepsy outcome

All patients received immunotherapy in the course of the disease: 19 out of 33 subjects were administered intravenous or oral steroids alone, whereas in 12 cases steroids were combined with intravenous immunoglobulin (IVIg) and in 4 with plasma exchange (PE) and IVIg. Two patients also received chronic treatment with azathioprine.

With regard to general clinical outcome, at last observation 20 (60.6%) patients did not report seizures, while the remaining 13 (39.4%) subjects had persistent seizures/epilepsy. Statistical analysis showed a significant association between unfavorable seizure outcome (defined as persisting seizures and development of chronic epilepsy) and delay in diagnosis ($p = .009$), low seizure frequency at onset ($p = .02$) and absence of amnestic syndrome ($p = .02$); absence/rarity of inter-ictal epileptic discharges on EEG appeared to be associated with unfavorable outcome even if this finding did not reach statistical significance ($p = .06$) (Table 3). No significant differences in terms of seizure/epilepsy outcome were observed between "seronegative" and "seropositive" patients; similarly no difference was detected by comparing patients treated with steroids alone and those treated with a combination therapy (steroids + IVIg or PE). Although a bilateral involvement of mesial temporal structures was associated with a worse

Table 1
General characteristics of population (N 33).

Demographic data		
Sex	Male (%)	19 (57.6%)
	Female (%)	14 (42.4%)
Age at disease onset	Mean age (SD; range)	61.2 years (SD = 15.3; range18–82)
Relevant data in past medical history		
Recent infections		8 (24.2%)
Previous neoplasms		6 (18.2%)
Clinical picture at first observation		
	Seizure (%)	33 (100%)
	Memory deficit (%)	30 (91%)
	Mood/behavioral changes (%)	22 (66.7%)
Seizure frequency at onset	Daily (cluster/SE) /weekly	27 (81.8%)
	Monthly/rare	6 (18.2%)
Sleep disturbances		10 (30.3%)
Laboratory and MRI findings		
AutoAbs profile (serum/CSF)		
	Positive	12 (36.4%)
	Anti-VGKC (LGI-1)	3
	Anti-VGKC (CASPR-2)	4
	Anti-NMDA	2
	Anti-SOX1	1
	Anti GAD65	1
	Anti-Hu/Anti-Ri	1
	Negative	21(63.6%)
Hypo Na +		7 (21,2%)
CSF findings		
	Normal	13 (39.4%)
	Hypercell/Hyperprot	10 (30.3%)
	Not available	10 (30.3%)
MRI findings		
	Normal	2 (6%)
	Hypersignal (T-mesial areas)	31 (94%)
	Unilateral T	9 (29%)
	Bilateral T/extraT	22 (71%)
MRI evolution (6–12 months)		
	Atrophy	12 (36.4%)
	Persistence of mild hypersignal	16 (48.5%)
	Normalization	5 (15.1%)
EEG data		
Interictal EEG pattern		
	Focal/diffuse slow activity	12 (36.4%)
	IED	21 (63.6%)
Ictal EEG	16 (48.5%)	
	Unilateral T	6 (37.5%)
	Bilateral T/biemispheric	10 (62.5%)
Dalay onset/therapy	1–2 months	20 (60.6%)
	> 3 months	13 (39.4%)
Therapy		
*Immunotherapy	Steroids (oral/iv)	19 (57.6%)
	Steroids + IVIG/TPE	14 (42.4%)
AEDs	monotherapy	20 (60.6%)
	polytherapy	11 (33.3%)
	none	2 (6.1%)
Follow up (months)	Mean/range	19 (SD = 11.7; range 12–60)
Clinical outcome at last available visit		
Epilepsy	Controlled seizures/SF	20 (60.6%)
	Persisting seizures	13 (39.4%)
Psycho-cognitive aspects	memory deficits	12 (36,4%)
	psychiatric disturbances	14 (42,4%)

*Immunotherapy schedule/cycles: IVIG 0.4/kg/day for 5 days; i.v. Steroids: 1 g/day for 3–5 days; oral Steroids: 1 mg/kg/day for 6 months; therapeutic plasma exchange (TPE): 3–5 days/week.

outcome in terms of cognitive and psychiatric sequelae, it did not seem to influence seizure/epilepsy outcome.

As far as psycho-cognitive aspects are concerned, at follow-up memory deficits and psychiatric disturbances were observed in 12 (36,4%) and 14 (42,4%) cases, respectively.

4. Discussion

Over the last ten years, identification of autoimmune forms of encephalitis related to antibodies directed against neuronal surface or intracellular antigens have shown that CNS disorders can be antibody-mediated and benefit from immunomodulatory therapies. In particular,

Table 2
Seizure semiology and intericatal/ictal EEG characteristics of LE population

Pts	Seizure semiology	EEG features	
		Interictal pattern/localization	Ictal pattern
1	Confusional state- irritability/anxiety - LC – oral/gestural automatisms – STCGS	θ-δ slow waves + IED / Bi T	DVR → rhythmic θ and δ over Bi T → HE
2	Facio-brachial dystonic seizures (FBDS)	θ-δ slow waves/ Bi T	DVR → rhythmic θ and δ over Bi T → L He
3	Viscerosensory symptoms - speech arrest	θ slow waves + IED/left T → right T	FVR → rhythmic θ → rhythmic sharp waves over L T
4	Viscerosensory symptoms - irritability/anxiety - oral automatisms – autonomic features (cardiac rythm changes)	θ-δ slow waves/right T → right HE	FVR → low voltage fast activity → rhythmic θ → rhythmic sharp waves over R T
5	Confusional state - irritability/anxiety - LC – STCGS	θ-δ slow waves/Bi T → Bi HE	DVR → rhythmic θ and δ over Bi T → HE
6	Viscerosensory symptoms/experiential phenomena - irritability/anxiety - LC - oral automatisms – STCGS - postictal amnesia	θ-δ slow waves/ Bi T → Bi HE	DVR → "δ brush" → rhythmic sharp waves → spike-and-waves over Bi T → HE
7	Viscerosensory symptoms/experiential phenomena - LC - oral/gestural automatisms - speech arrest	IED /left T → Bi T	FVR → low voltage fast activity → rhythmic θ → rhythmic sharp waves over L T
8	Viscerosensory symptoms - LC - autonomic features (piloerection)	θ-δ slow waves + IED/left T	FVR → rhythmic θ and δ → rhythmic sharp waves → spike-and- waves over L T
9	Viscerosensory symptoms/experiential phenomena - autonomic features (piloerection) speech arrest	θ slow waves + IED/Bi T	FVR → "δ brush" → rhythmic sharp waves over Bi (> L) T
10	Confusional state - LC - speech arrest - STCGS postictal amnesia	θ-δ slow waves + IED/left T → Bi HE	FVR → rhythmic θ and δ over Bi T → F
11	Confusional state - LC - irritability/anxiety – STCGS	θ slow waves/left T → Bi T	NR
12	Confusional state - irritability/anxiety - LC - oral/gestural automatisms - speech arrest - postictal amnesia	θ-δ slow waves/left T → Bi T θ-δ slow waves/Bi HE	FVR → rhythmic θ and δ → rhythmic sharp waves over Bi T → Bi P
13	Viscerosensory symptoms - confusional state - LC - speech arrest - oral automatisms	θ slow waves + IED /left T	NR
14	Facio-brachial dystonic seizures (FBDS)	θ slow waves/left T → Bi T	DVR → rhythmic θ and δ over Bi T → HE
15	Viscerosensory symptoms - LC - oral automatisms	θ slow waves + IED/right T and F	NR
16	Viscerosensory symptoms - speech arrest - LC - postictal amnesia	θ slow waves + IED/left T → Bi T	NR
17	Confusional state - LC - speech arrest - STCGS- postictal amnesia	θ slow waves + IED/ Bi T	FVR → rhythmic θ and δ → rhythmic sharp waves over Bi (> L) T
18	Confusional state - LC - oral automatisms -STCGS - postictal amnesia	θ slow waves + IED/left T → Bi T	FVR → rhythmic θ and δ → rhythmic sharp waves over L T → R F-T
19	Confusional state - LC - STCGS	θ slow waves/ Right T	NR
20	Viscerosensory symptoms - speech arrest - LC - postictal amnesia	θ slow waves/Bi T	NR
21	Confusional state - speech arrest - (LC)	θ slow waves + IED/left T	NR
22	Viscerosensory symptoms - speech arrest - LC - oral/gestural automatisms - postictal amnesia	θ slow waves + IED/right T	NR
23	Confusional state - complex movement disorders (facial/gestural automatisms)	Diffuse θ slow waves/recurrent burst suppression pattern	DVR → "δ brush"/ recurrent burst suppression pattern over Bi T → HE
24	Arrest of ongoing activity - LC - altered facial expression - red eyes – vocalization - gestural automatisms	IED / Bi T > left	NR
25	Confusional state - viscerosensory symptoms	θ slow waves + IED/ Right T → Bi T	NR
26	Confusional state-LC-TCGS	θ-δ slow waves + IED /Bi HE	NR
27	Confusional state-Viscerosensory symptoms-anxiety	θ slow waves/ Right T → Bi T	NR
28	Viscerosensory symptoms-complex movement disorders(facial/oral automatisms)-allucinations	θ slow waves + IED / Right T → Bi T	NR
29	"Grimacing"-altered facial expression-ipertonic muscular tone-laughing-flushing-phasic disorders	θ-δ slow waves + IED/Left T	NR
30	Viscerosensory symptoms-speech arrest-LC-STCGS-postictal amnesia	θ-δ slow waves + IED/Left T	NR
31	Sensory symptoms-LC-STCGS-postictal amnesia	θ-δ slow waves+ IED /Bi T	NR
32	Viscerosensory symptoms-speech arrest-LC	θ-δ slow waves Left T	NR
33	Viscerosensory symptoms-speech arrest-LC-STCGS-postictal amnesia	θ-δ slow waves + IED/Left T → Bi T	FVR → rhythmic θ and δ over L T → Bi T

BiT = bitemporal; F = frontal; IED = Interictal Epileptiform Discharges; DVR = Diffuse Voltage Reduction; FVR = Focal Voltage Reduction; HE = hemispheric; L = Left; LC = loss of consciousness; NR = not recorded; P = parietal; R = Right. STCGS = secondary generalized tonic-clonic seizures; T = temporal; θ = theta; δ = delta.

it has become increasingly clear that in case of epilepsy related to autoimmune process, conventional anticonvulsants cannot control seizures, and immunotherapy can represent both etiological and symptomatic treatment [1–7].

Until today, in spite of the expanding knowledge of these conditions, some crucial aspects have not been fully elucidated. First of all, in clinical practice the definition of disease stage and prognosis might be challenging, especially in those cases in which immunotherapy does not allow complete recovery [24]. Indeed, in a significant proportion of patients, persisting seizures and/or psycho-cognitive symptoms can be observed, and it is often difficult to establish whether such clinical manifestations are the expression of an active immune-mediated process or represent long-term sequelae of an "extinguished" condition. As regards seizures, an inflammatory disease usually determines an initial tissue damage, which might be followed, in some cases, by an epileptogenic process leading to the development of chronic epilepsy. Indeed, it is not rare that temporal lobe seizures recur even if all clinical and instrumental (neuroimaging and laboratory) data suggest a complete resolution of the acute/subacute phase [8,9,25,26,27].

However, early factors predisposing to chronic epilepsy have not been specifically identified so far.

Despite the methodological limitations of our study, some data appear noteworthy, the most important being that patients with low seizure frequency at disease onset, absence of defined amnestic syndrome as well as absence/paucity of IED on EEG recordings showed an unfavorable seizure outcome and developed chronic, often drug-resistant epilepsy. It might be argued that an insidious clinical picture could hamper diagnosis, leading to a therapeutic delay, which is likely to negatively affect clinical course. In support of this hypothesis, we found that those patients with a "definite" limbic syndrome and more severe

Table 3
Clinical, diagnostic and laboratory data/findings.

	Seizure/epilepsy outcome		
	Persisting Seizures	**No seizures**	***P* value**
History of recent infective/ inflammatory disease			
Yes	2	6	$P = 0.95$
No	11	14	
History of neoplasms°			
Yes	3	3	$P = 0.56$
No	10	17	
Cognitive disturbances (Memory functions)°			
Yes	10	20	**P = 0.02**
No	3	0	
Mood/behavioral changes°			
Yes	9	13	$P = 1.0$
No	4	7	
Seizures/paroxysmal movement disorders° frequency at onset			
Daily/Weekly	8	19	**P = 0.02**
Monthly/rare	5	1	
Other signs/symptoms° (Sleep disorders/autonomic alterations)			
Yes	6	4	$P = 0.14$
No	7	16	
Interictal/ictal EEG°			
IED/Seizures	6	15	**P = 0.06**
No IED/no seizures	8	4	
MRI typical alterations°			
Yes	12	19	P = 1.0
No	1	1	
Autoab profile			
Positive	5	7	P = 1.0
Negative	9	12	
Disease duration at time of diagnosis/treatment°			
1–-2 months	4	16	**P = 0.009**
> 3 months	9	4	

All results were considered significant at $P < .05$ (*).
Fisher's exact test was used instead of Chi square test according to the patients' distribution in the cells.

disease presentation showed better seizure outcome. Indeed, the early recognition of a potentially reversible condition, such as LE, is always crucial for appropriate targeted treatment, and it is associated with better clinical outcome [24,28,29].

As regards the other clinical and diagnostic (neuroimaging and laboratory) features, traditionally considered as consistent markers of disease, no significant correlation with long-term epilepsy/seizures outcome was found.

In line with the results obtained in our study, from an operative point of view, it could be wise to maintain a high level of neurological surveillance in case of subacute onset of temporal lobe seizures, especially in the elderly, even if other crucial clinical or laboratory markers of LE - including cognitive impairment, psychiatric disturbances or Abs detection - are lacking.

Indeed, although recent attempts of providing clinical scores and scales could facilitate an early recognition [10,27,30], in clinical practice a diagnostic delay is frequently observed, particularly in those conditions with subtle clinical presentation at onset [27,32].

In spite of some interesting suggestions, this study appears to be limited by several factors including its retrospective nature, the small sample size and the heterogeneity of the enrolled cohort in terms of time at first observation, anatomical damage documented by MRI, Abs profile, therapeutic schemes and psycho-cognitive evaluations. Considering these limitations, our preliminary results cannot allow us to draw any definitive conclusions, and longitudinal studies on larger samples are still warranted.

In conclusion, our study seems to provide interesting data suggesting that the "mild" forms of LE may be more insidious if compared with "definite" and explosive conditions in terms of seizure/epilepsy outcome. This observation could be explained by the diagnostic delay induced by the atypical/mild clinical presentation at onset. Indeed, in such condition the consequent therapeutic delay likely facilitates an inflammation-mediated epileptogenic process leading to chronic epilepsy. The final consideration is that subtle LE may be a pitfall in clinical practice, highlighting the need for a better knowledge of the clinical spectrum of these not so rare entities.

Declarations of interest

None.

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