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Nonlesional late-onset epilepsy: Semiology, EEG, cerebrospinal fluid, and seizure outcome characteristics☆

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ABSTRACT

Introduction: Incidence and prevalence of epilepsy increase with advancing age. Although the majority of late-onset epilepsies are of lesional origin, a considerable proportion of patients present with unknown etiology. The aim of this study was to evaluate the semiological, electroencephalographic (EEG), and cerebrospinal fluid (CSF) characteristics as well as the 12-month seizure outcome in a cohort of patients with nonlesional late-onset epilepsy (≥55 years).

Method: A total of 54 patients with newly diagnosed nonlesional late-onset epilepsy (NLLOE) were retrospectively evaluated for seizure type using the most recent International League Against Epilepsy (ILAE) classification of seizure types, EEG characteristics, and CSF profile and followed-up for at least 12 months after epilepsy onset. Results were compared with a gender-matched control group of 58 patients with nonlesional early-onset epilepsy (NLEOE).

Results: The predominant seizure types in NLLOE were focal to bilateral tonic–clonic seizures (30%) as well as focal onset impaired awareness motor seizures (IAMS) (22%) and focal onset impaired awareness nonmotor seizures (IANMS) (22%). The predominant seizure types in NLEOE were focal to bilateral tonic–clonic seizures (43%) as well as focal onset aware nonmotor seizures (ANMS) (31%) and IAMS (31%). Focal onset impaired awareness nonmotor seizures were found to be more characteristic in patients with NLLOE ($p = 0.019$; $\alpha < 0.05$; NLLOE: 22.2% vs. NLEOE: 8.6%). Electroencephalography revealed no significant differences between groups. Of interest, three patients with NLLOE (8%) presented with oligoclonal bands (OCB) in CSF albeit absence of antineuronal antibodies. Seizure-free rate was 70%. Adverse effects from medication leading to antiepileptic drug (AED) change were reported in 12 patients (22%), valproate was the best tolerated AED in patients with NLLOE [adverse effects in 9%, compared with 12% (gabapentin) and 26% (levetiracetam)].

Conclusions: Using the most recent classification system, different patterns of semiological characteristics were identified: NLLOE more frequently present with IANMS, whereas patients with NLEOE rather have ANMS. Oligoclonal bands were only detected in patients with NLLOE, indicating that careful exclusion of autoimmune encephalitis in this patient group is warranted. Our findings may help to more accurately identify and characterize patients with NLLOE to improve targeted diagnostics and adequate treatment in this challenging group of patients.

1. Introduction

Epilepsy is one of the most frequent neurological diseases with a cumulative incidence of 3–10% [1]. The incidence of unprovoked seizures in patients aged >65 years is 139 per 100,000 [2]. Thus, given the increase of individuals >65 years in terms of relative and absolute numbers worldwide, the incidence of epilepsy is expected to rise dramatically in our population. A lower incidence of generalized tonic–clonic seizures and a higher frequency of simple motor and/or sensory symptoms in late-onset epilepsy may lead to misdiagnosis of dementia or stroke [3]. Furthermore, because of a higher rate of comorbidities in elderly patients, subtle seizure phenomena may falsely be attributed to other comorbidities [3]. Consequently, a more thorough understanding of seizure characteristics in older adults will improve the rate of correct diagnosis, especially in patients with inconspicuous brain imaging.

Previous studies on seizure semiology in elderly patients specifically focused on the comparison with younger patients with epilepsy irrespective of the underlying etiology [4–6]. Tanaka et al. reported cerebrovascular diseases (15.7%), dementia (10%), inflammatory disorders (8.6%), and brain tumors (4.3%) to be the most common etiologies in

Abbreviations: NLLOE, nonlesional late-onset epilepsy; NLEOE, nonlesional early-onset epilepsy; FBTC, focal to bilateral tonic–clonic; IAMS, focal onset impaired awareness motor seizure; IANMS, focal onset impaired awareness nonmotor seizure; ANMS, focal onset aware nonmotor seizure.

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their cohort of 70 patients with epilepsy onset at the age of 65 years or older [7]. In the same age group, Stefan et al. found cerebrovascular diseases in about one-third of their patients [5]. Nevertheless, 25% to 53% of late-onset focal epilepsies are still considered to be of nonlesional origin [5, 7, 8]. Whereas seizure semiology in lesional epilepsies essentially depends on type and localization of the structural brain abnormality, no conclusions on semiology and topographical representation can be drawn in nonlesional cases. However, the relevance of semiological characteristics in the context of diagnostic workup in nonlesional late-onset epilepsy (NLLOE) patients has not yet been systemically investigated.

This study aimed to evaluate semiological characteristics in a cohort of patients with NLLOE compared with a group of patients with nonlesional early-onset epilepsy (NLEOE) using the most recent semiological International League Against Epilepsy (ILAE) classification proposed by Fisher and colleagues [9]. Furthermore, patients with NLLOE were characterized regarding their cerebrospinal fluid (CSF) profiles, electroencephalographic (EEG) characteristics, and seizure-free rate after 12-months of follow-up.

2. Materials and methods

We conducted a retrospective single center observational study. The gender-matched control group of patients with NLEOE was also identified retrospectively. All data were obtained during clinical routine.

The local Institutional Review Board approved this study. Between April 2011 and January 2016 patients newly diagnosed with NLLOE (age at epilepsy onset ≥55 years) at the University Hospital of Greifswald/Germany were included. Patients with (1) a newly diagnosed seizure disorder, (2) an age at epilepsy onset of ≥55 years, (3) no potentially epileptogenic lesion on brain imaging (magnetic resonance imaging (MRI) (1.5 or 3 Tesla) or computer tomography (CT) if an MRI was not possible for medical reasons), and (4) no evidence of antineural and neuronal antibodies in serum and CSF were included (NLLOE). The control group (NLEOE) consisted of patients with a newly diagnosed seizure disorder and age at epilepsy onset <55 years, nonlesional brain imaging (MRI), and no clinical evidence of autoimmune origin. Serum and CSF analysis was performed in all patients and controls; however, antibody testing in patients with NLEOE is not clinical routine and was only performed in cases of clinical need (such as additional subacute short-term memory deficits).

Clinical data were collected by reviewing the patients' medical records and by taking medical history of the patient or witnesses of the suspected seizure. On the basis of this information, all seizures were retrospectively classified according to the International League Against Epilepsy (ILAE) operational classification of seizure types from 2017 (Table 1) [9]. In short, focal onset seizures were classified in (1) *aware* and *impaired awareness* seizures and (2) *nonmotor* (auras) [autonomic, behavioral arrest, cognitive (aphasia, déjà-vu, apraxia, hallucinations), emotional and sensory (epigastric, olfactory, or gustatory auras, paresthesia)] or *motor* seizures [automatisms (oral and/or manual), tonic, clonic, hyperkinetic, myoclonic, or epileptic spasms)]. Focal onset seizures with neither clear motor nor nonmotor symptoms were considered as focal onset impaired awareness seizures and not further subclassified. We added additional semiological characteristics, such as tongue bite, initial cry, aching muscle, vegetative symptoms (hypersalivation, tachycardia), and enuresis and/or encopresis as well as status epilepticus (SE) and various manifestation of Todd's phenomenon to the existing classification.

First inpatient assessment included routine EEG (International 10-to-20-system of electrode placement), MRI, and/or CT investigations as well as collection of serum and CSF in all patients. Cell counts were determined microscopically within the first 2 h after lumbar puncture using a Fuchs-Rosenthal counting chamber. Lactate was measured by an enzymatic optical test at the Dimension Vista 1500 (Siemens Healthcare, Eschborn, Germany). Albumin, Immunoglobulin G, A, and M from paired serum and CSF samples were analyzed by nephelometry (ProSpec, Siemens Healthcare Diagnostics, Marburg, Germany). Lactate and albumin were investigated within 2 h after lumbar puncture. The intrathecal Ig detection was calculated according to Reibergram calculations [10]. Oligoclonal bands (OCB) were determined by immunofixation with a semiautomated agarose electrophoresis system (Hydragel 9 CSF, Sebia Hydrasys 2Scan, Sebia GmbG, Fulda, Germany) [11]. Interpretation of OCB was done blinded for each pattern by two experienced raters followed by consensus decision; OCB type was classified according to Andersson et al. [12]; OCB positivity was assumed with the detection of ≥2 bands in CSF.

Table 1
Detailed information on seizure characteristics and semiology of patients with NLLOE and NLEOE using the semiological classification proposed by Fisher et al. [9].

Seizure types	NLLOE % (n=)	NLEOE % (n=)	α = 0.05
N=	54	58	
Focal onset	0%	0%	
Focal onset aware	0%	0%	
Focal onset aware motor (AMS)	0%	5.1% (3)	0.173
Focal onset aware nonmotor (ANMS)	14.8% (8)	31% (18)	0.102
Focal onset impaired awareness (IAS)	18.5% (10)	8.6% (5)	0.056
Focal onset impaired awareness motor (IAMS)	22.2% (12)	31% (18)	0.392
Focal onset impaired awareness nonmotor (IANMS)	22.2% (12)	8.6% (5)	0.019
Generalized onset	0%	1.7% (1)	0.561
Generalized onset motor (GMS)	20.3% (11)	18.9% (11)	0.348
Generalized onset nonmotor	0%	3.4% (2)	0.313
Focal to bilateral tonic–clonic (FBTC)	29.6% (16)	43.1% (25)	0.290
Unknown onset	0%	0%	
Unknown onset motor	0%	0%	
Unknown onset nonmotor	0%	0%	
Motor			
Automatism	14.8% (8)	13.8% (8)	0.545
Atonic	0%	1.7% (1)	0.518
Clonic	16.7% (9)	22.4% (13)	0.300
Epileptic spasms	0%	0%	
Hyperkinetic	1.9% (1)	8.6% (5)	0.120
Myoclonic	1.9% (1)	5.2% (3)	0.337
Tonic	16.7% (9)	8.6% (5)	0.159
Nonmotor			
Autonomic	0%	3.4% (2)	
Behavioral arrest	0%	1.7% (1)	
Cognitive	27.8% (15)	37.9% (22)	0.174
Emotional	5.6% (3)	15.5% (9)	0.080
Sensory	11.1% (6)	19.0% (11)	0.186
Status epilepticus	11.1% (6)	6.9% (4)	0.326
Todd paresis	16.7% (9)	12.1% (7)	0.335
Additional symptoms	44.4% (24)	36.2% (21)	0.243

NLLOE: nonlesional late-onset epilepsy, NLEOE: nonlesional early-onset epilepsy.

All patients with NLLOE as well as 17% of the patients with NLEOE were tested for serum and CSF antibodies against glutamic acid decarboxylase 65 (GAD65), *N*-methyl-D-aspartate receptor (NMDAR), γ-amino-butyric acid B receptor (GABA(B)R), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors 1/2 (AMPA1/2), dipeptidyl-peptidase-like protein-6 (DPPX), metabotropic glutamate receptor 5 (mGluR5), leucine-rich glioma inactivated 1 (LGI1) protein, contactin-associated protein-like 2 (CASPR-2), voltage-gated potassium complex (VGKCc) antigens, glycine receptors (GlyRs), and atypical antibodies against neuropil (MVZ Labor Krone GbR, Siemensstraße 40, 32105 Bad Salzuflen, Germany).

Immunosuppressive and/or antiepileptic drug (AED) therapies were started as recommended by the treating Neurology consultant. Patients with NLLOE were followed up for a minimum of 12 months after diagnosis. Seizure-free outcome was defined as “seizure-free period for at least nine months”.

For statistical processing of the data, SPSS 23.0 (IBM Co., Armonk, New York, USA) was used. Statistical significance was assessed using Chi-square test and Fisher's exact test for nominal data. Intergroup comparison (NLLOE and NLEOE) was performed using the Mann–U–

Whitney test (no Gaussian distribution of data). P values ≤ 0.05 were regarded as statistically significant.

3. Results

Of 121 patients screened, 54 (29 female, 54%) met the inclusion criteria and were enrolled in the study. Their mean and median age was 78 years (standard deviation (SD) ± 8.01), and their mean age at epilepsy onset was 76 years (SD ± 8.33) (median age 77 years). The control group consisted of 58 patients with NLEOE (36 female, 62%) with a mean age of 44 years (SD ± 12.05) (median age 44.5 years) and a mean age at epilepsy onset of 31 years (SD ± 13.35) (median age 30 years).

3.1. NLLOE

Detailed information on seizure characteristics and semiology of patients and controls are given in Table 1.

Focal to bilateral tonic–clonic (FBTC) seizures were the most frequent seizure type (n = 16, 29.6%) as well as focal onset impaired awareness motor seizures (IAMS; n = 12, 22%) and focal onset impaired awareness nonmotor seizures (IANMS; n = 12, 22%). Fifteen of the 54 patients (28%) suffered from ≥2 different seizure types.

The majority of patients with focal onset motor seizures reported clonic (17%; n = 9) and tonic symptoms (17%; n = 9) as well as automatisms (15%; n = 8). Cognitive impairment (aphasia, apraxia, déjà vu, and/or hallucinations) (28%; n = 15) followed by sensory symptoms (epigastric, gustatory, olfactory auras, and paresthesia) (11%, n = 6) were the most frequent nonmotor symptoms. Status epilepticus occurred in 11% (n = 6) and symptoms of Todd's phenomenon in 17% (n = 9) of our patients. Twenty-four patients (44%) reported additional features, such as occasional tongue bite, initial cry, aching muscles, enuresis and/or encopresis, and/or vegetative symptoms (e.g., hypersalivation or tachycardia).

Routine EEG investigations were performed in all of our patients, 22 of them (41%) had EEG abnormalities: epileptic discharges (ED; sharp waves and sharp-slow-waves) were found in nine patients (generalized ED n = 2); nine patients had intermittent or continuous regional slow activity (five of them with intermittent regional ED), and 13 patients had intermittent generalized slow activity (classified as encephalopathic EEG).

3.2. NLEOE

Twenty-five (43%) of our patients with NLEOE had FBTC seizures, followed by focal onset aware nonmotor seizures (ANMS, n = 18, 31%) and IAMS (n = 18, 31%). Twenty-six of 58 patients had ≥2 seizure different seizure types. The most common motoric features were clonic seizures (n = 13; 22%) and automatisms (n = 8, 14%), whereas cognitive impairment (n = 22; 38%), sensory (n = 11; 19%), and emotional symptoms (n = 9; 16%) were common nonmotor symptoms. Four patients with NLEOE (7%) had at least one SE, 7 patients (12%) Todd's phenomenon, and 21 patients (36%) reported additional symptoms, such as tongue bite, initial cry, aching muscles, enuresis and/or encopresis, and/or vegetative symptoms (e.g., hypersalivation or tachycardia).

Routine EEG was performed in 56 of 58 controls (97%), 27 of them (48%) had abnormal EEG findings: ED were found in 10 patients (generalized ED n = 1); 15 patients had intermittent or continuous regional slow activity (four of them with intermittent regional ED), and 3 patients had intermittent generalized slow activity (classified as encephalopathic EEG).

3.3. Intergroup comparison: semiological characteristics and EEG

Focal onset impaired awareness nonmotor seizures were found to be more characteristic in patients with NLLOE, as compared with patients with NLEOE ($p = 0.019$; $\alpha < 0.05$; NLLOE: 22.2% vs. NLEOE: 8.6%). Twelve patients in the cohort with NLLOE presented with IANMS; seven of them underwent neuropsychological evaluation, of which two patients had Alzheimer disease, one presented with mild cognitive impairment, one with depression, and three patients with an age-appropriate inconspicuous neuropsychological profile. One patient was known to have dementia before epilepsy onset.

Intergroup comparison revealed no significant differences between groups for other semiological or EEG characteristics.

3.4. Intergroup comparison: CSF results

Increased CSF levels of total protein (>500 mg/dl) and lactate (>2.5 mmol/l) were significantly more common in the group with NLLOE (total protein: 57% in NLLOE vs. 26% in NLEOE; lactate: 15% vs. 7%, respectively; all P's < 0.0001). Pleocytosis (>4 Mpt/l) was found in 7% of NLEOE (n = 4) and in none of the patients with NLLOE.

OCB analysis was conducted in 74% (n = 40) of the patients with NLLOE and in 91% (n = 53) of the patients with NLEOE. None of our patients with NLLOE and NLEOE had quantitative intrathecal immunoglobulin synthesis [10], whereas OCB in CSF were found only in NLLOE cases (8%; n = 3). *Patient #1* (female, 71 y) had recurrent epileptic seizures (IAS and IAMS) with postictal confusion; retrospective analysis revealed no other reason for OCB positivity than epilepsy. This patient became seizure-free with a monotherapy of levetiracetam (2000 mg daily). *Patient #2* (female, 84 y) had recurrent epileptic seizures (ANMS with epigastric aura, FBTC seizures with postictal confusion); in addition to OCB detection, the patient had a positive measles-rubella-zoster (MRZ) reaction (composed of the three antibody indices against measles, rubella, and varicella zoster virus). This patient became seizure-free with a monotherapy of levetiracetam (1500 mg daily). *Patient #3* (male, 67 y) had ANMS, FBTC seizures, and recurrent SE with progressive delirant symptoms. This patient was drug-resistant with continuing seizures despite a combination of four AED and immunosuppressive therapy with prednisolone (1 mg/kg body weight). Follow-up revealed unilateral hippocampal atrophy in MRI, classifying this epilepsy as "lesional" during the course of the disease. This patient died because of complications of SE within one year after epilepsy onset.

3.5. Outcome

A 12- month follow-up was available in 43 of 54 patients with NLLOE (80%). Eleven patients were lost to follow-up, six of them died within one year after epilepsy onset, one of them during SE, the remaining five patients could not be reached for follow-up because of unknown reasons. Among the 43 patients, 30 (70%) were seizure-free after 12 months of follow-up, 25 of them (83%) with the first AED, another three patients (10%) after AED modification and two patients (7%) without AED. Twelve patients (28%) had ongoing seizures despite medication and one patient because of AED noncompliance. Among patients with SE, one third died before follow up, one third became seizure-free. The majority of patients (67%; n = 29) were treated with AED in monotherapy (56% of them with levetiracetam) (two AEDs: 19%, n = 8; ≥2 AEDs: 9%, n = 4). Levetiracetam (54%; n = 23) was the most commonly prescribed AED, followed by gabapentin (40%; n = 17), and valproic acid (21%, n = 9). Adverse effects from medication leading to AED change were reported in 12 patients (22%), valproate was the best tolerated AED in our group with NLLOE [adverse effects in 9%, compared with 12% (gabapentin) and 26% (levetiracetam)].

4. Discussion

The aim of this retrospective, observational cohort study was to identify semiological characteristics in patients with NLLOE compared with a group of patients with NLEOE. We further aimed to evaluate CSF profiles, EEG characteristics, and the outcome after a follow-up of

at least 12 months in this highly selective group of patients. Patients aged >55 years were included into the study, because of the known sharp rise in incidence of unprovoked seizures in this age group [1, 13]. To our knowledge, this is the first study comparing patients with nonlesional epilepsy with early and late-onset with regard to these characteristics using the most recent operational classification of seizure types by the ILAE proposed by Fisher and colleagues [9].

In our sample of patients with NLLOE, IANMS were the predominant seizure type in comparison with that from patients with NLEOE ($p = 0.019$) with an often very subtle semiology. In contrast, patients with NLEOE rather presented with ANMS and IANMS as well as focal to bilateral tonic–clonic seizures. In both groups, most frequent motor symptoms were clonic/tonic movements and automatisms, while nonmotor seizures frequently presented with cognitive and sensory symptoms. With regard to CSF results, OCBs were found in 3 patients, all of them in the group with NLLOE. Electroencephalographic analysis revealed no differences between both groups. After a follow-up of 12 months, 70% of our NLLEO patients were seizure-free.

Prior studies on semiological features in late-onset epilepsies considered all etiologies and did not specifically focus on nonlesional cases, the target group of this study [3, 7, 14–16].

The often subtle semiology of IANMS and the lack of features that are commonly known to be associated with epileptic seizures (such as tonic–clonic movements) could lead clinicians to an incorrect diagnosis of seizures as psychiatric disorders including dementia, metabolic disorders, or transient ischemic attacks [14, 17]. At the same time, other conditions with high prevalence in the elderly, such as hypertension, stroke, cardiac diseases, or dementia must be considered in the diagnostic workup of these patients, as they may exhibit similar clinical features but require a different diagnostic and therapeutic approach [14]. Focal onset impaired awareness nonmotor seizure — often accompanied by ictal and postictal episodic inadequate behavior and/or confusion and memory loss — may, therefore, be misinterpreted as mild cognitive impairment as described in incipient dementia [18, 19], especially in cases with recurrent seizures and/or prolonged postictal state. Postictal states with prolonged episodes of altered mental state in patients with NLLOE may even obscure or delay the diagnosis.

Huang et al. reported a high rate of structural brain pathologies in elderly patients to be responsible for the high proportion of complex partial seizures in this group [15]. Whereas in cases with defined structural brain abnormalities the association with seizure semiology is often identifiable, the high incidence of IANMS among our patients with NLLOE suggests a role of subtle lesions that are not detectable on standard neuroradiological MRI evaluation. Shasha et al. suggested various conditions associated with neurodegenerative diseases, such as β-amyloid deposition, neuronal loss, and gliosis as well as alterations in neurotransmitters and changes in cellular excitotoxicity to contribute to epileptogenesis [20]. However, the exact mechanisms of cortical neurodegeneration and their epileptogenic potential are not clearly understood.

In addition to differentiating post-ictal states from incipient dementia, physician should be aware of the high proportion of elderly patients with a coincidence of dementia and epilepsy. Individuals with dementia suffer from a five-to-tenfold increased risk for epilepsy, as compared with age-matched controls [17, 21], suggesting that neurodegeneration induces microlesions, with an increased epileptogenic potential that may not be localizable on MRI. On the other hand, the effect of recurrent seizures on the cognitive abilities is unclear. Taken together, comprehensive knowledge about seizure semiology and particularly subtle signs of seizures in patients with late-onset epilepsy will greatly aid correct diagnosis. This issue is of high clinical relevance, because a successful AED treatment is possible in the majority of patients [22]. Therefore, education of relatives and, for example, employees in care facilities should be part of a comprehensive care concept. In cases with diagnostic uncertainty, long-term or video-EEG monitoring may provide crucial information.

Our results show interesting aspects on CSF changes when comparing patients with early- and late-onset epilepsy. Increased CSF levels of protein and lactate are age dependent phenomena [23, 24] and have been associated with epileptic seizures as well as the occurrence of postictal pleocytosis [25–27]. In our study, OCB in CSF were found in three patients, but only in the NLLOE group (8%). In a very recent study, Fauser et al. reported intrathecal immunoglobulin G synthesis in 8% of patients with epilepsies of unknown etiology, which is consistent with our findings [28]. In contrast, Kowski et al. reported intrathecal immunoglobulin synthesis in 34% of their patients with cryptogenic epilepsy [29]. Notwithstanding different data on the prevalence, the proof of intrathecal immunoglobulin synthesis can suggest an autoimmune origin of epilepsy [30]. Among our three patients with NLLOE with OCB in CSF, one patient (#3) fulfilled the criteria of autoantibody-negative but probable autoimmune encephalitis according to the recently published classification by Graus and colleagues [30]. This patient presented with recurrent refractory SE, psychiatric symptoms, unilateral hippocampal atrophy in MRI, and died within one year after epilepsy onset. Change of etiology from nonlesional to lesional during the course of the disease may be due to an autoimmune etiology, even though no autopsy was done to confirm this hypothesis in this special case. Furthermore, degenerative hippocampal sclerosis of aging can cause symptoms of dementia, but usually lack epileptic seizures [31, 32]. Therefore, a shift towards a lesional epilepsy should be considered and should be part of the diagnostic concept, especially in patients with AED-refractory epilepsy.

The other two OCB positive patients had no additional evidence of autoimmune encephalitis and became seizure-free within one year after epilepsy onset. However, the small number of OCB positive patients in our sample precludes further subgroup analyses on the pathogenetic relevance of OCB in epilepsy. Very recently, von Podewils et al. reported autoimmune etiology, more precisely limbic encephalitis, in 6% of their cohort of 66 patients with new-onset seizures above the age of 55 years [33]. Risk was increased in patients between 55 and 65 years and in those with concomitant depression. These findings suggest that in patients with late-onset epilepsy and suspicious autoimmune origin, testing for antibodies targeting neural antigens should be considered in the diagnostic protocol, especially in cases with concomitant psychiatric symptoms, such as depression or behavioral impairment.

The relatively high incidence of SE in our cohort with NLLOE of 11% is significant in terms of the negative economic impact of SE and substantial impairments in the individual quality of life [34, 35]. One-third of our patients with SE died, which is in line with the overall hospital mortality of SE of about 15–20% [35].

The seizure-free rate of 70% among our patients with NLLOE is consistent with findings of prior studies on the outcome in late-onset epilepsy; Tanaka et al. reported a seizure-free rate under monotherapy of 78% in his group of patients with late-onset epilepsy with various etiologies [7]. It can, therefore, be assumed that late-onset epilepsies respond well to AED treatment and that the etiology does not impact the first year outcome in elderly patients. When choosing an AED in elderly patients, different aspects such as hepatic metabolism (valproate, phenytoin), enzyme induction (carbamazepine, phenytoin), and nonlinear pharmacokinetics (phenytoin) as well as drug interactions and adverse effects on cognition (primidone, phenobarbital, topiramate, zonisamide) have to be considered [36]. An interesting finding of the present study is that although levetiracetam was highly effective in this patient group, about a quarter of the patients reported adverse effects, supporting findings of other studies on adverse effects in this age group [37]. The lowest rate of adverse effects was seen with valproic acid in patients with NLLOE. However, other reports do not agree with this finding [8], so this issue should be followed up in larger cohorts.

Several limitations of our study have to be considered in interpretation of our results. First, because of the selective inclusion criteria, our cohort was relatively small; therefore, associations between

characteristic features may have been missed. On the other hand, strict exclusion of lesional etiology of seizure yielded a homogeneous sample not available in most of the larger studies. Second, because of the retrospective design of the study, information on seizure semiology was taken from personal and external descriptions. Presumably, in prospective approaches video-EEG monitoring would help to correctly define semiology. Third, not all of our patients with NLEOE (control group) underwent antibody testing in serum/CSF, and not all patients with NLLOE had OCB analysis, so that the presence of antibody or OCB positivity in this, patients cannot be excluded. However, we excluded autoimmune encephalitis using anamnestic (patient interview) and apparative (EEG, MRI, CSF) data in all patients. Fourth, neuropsychological evaluation of all patients was not available, so that the prevalence of dementia as a confounding factor cannot be evaluated. The associations between NLLOE and dementia and between autoimmune encephalitis and dementia will be a focus of future research.

5. Conclusions

Several semiological, EEG, and CSF characteristics in NLLOE were described in the present study. Patients with NLLOE predominantly presented with IANMS and more frequently showed OCB in CSF. Presence of OCB in CSF should guide clinicians to initiate further diagnostic steps to exclude an autoimmune etiology, including testing for serum and/or CSF antibodies. One-year seizure-free rate in patients with NLLOE under AED was 70%; however, although highly effective, the adverse effect rate under levetiracetam was relatively high, rather suggesting the use of valproic acid in this group.

Given the rising number of patients with late-onset epilepsies due to demographic changes, with a considerable proportion of nonlesional cases, the identification and characterization of epileptic seizures is crucial to guide targeted diagnostics and adequate treatment in this cohort. Education of relatives, physicians, and care givers should be part of a comprehensive care concept to improve both the overall treatment success and quality of life of these patients.

Ethics statement

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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Author contribution statement

MS and FvP generated the research idea, study design, and concept. LH, MS, and FvP acquired and analyzed the data and drafted the work. MS, AF, and FvP made critical revisions for important intellectual content and interpreted the data. LH, MS, and FvP wrote the manuscript. LH, MS, AF, and FvP approved the final manuscript.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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