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ORIGINAL ARTICLE

Etiological diagnosis of late-onset epilepsy: A key priority for Italian epileptologists – Insights from a LICE survey

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Abstract

Objective: The incidence of epilepsy rises markedly after age 50. While late-onset epilepsy (LOE) is often linked to structural brain abnormalities, non-structural factors, such as infections, autoimmune disorders, and neurodegenerative diseases, also contribute. Approximately 20% of LOE cases remain of unknown etiology (LOEU). This study evaluated the diagnostic and therapeutic strategies employed by Italian epileptologists in managing LOE and LOEU, with the ultimate goal of proposing a standardized diagnostic algorithm.

Methods: Data were collected through a cross-sectional online survey administered to neurologists who are formal members of the Italian Chapter of the International League Against Epilepsy (LICE). Descriptive statistics were used to summarize responses, and inferential statistics were applied to derive meaningful conclusions.

Elena Nardi Cesarini and Giovanni Falcicchio contributed equally to the work.

Results: Sixty-five epilepsy centers across 19 of the 20 Italian regions participated in the survey. EEG (100%; $n = 65$) and brain MRI (92.31%; $n = 60$) were routinely employed in the diagnostic evaluation of LOE. In over half of the centers (58.46%; $n = 38$), sleep-activated or sleep-influenced EEGs were also used. For LOEU cases, neuropsychological assessments were performed in 60% of centers. More than 30% of centers employed additional diagnostic tools, including lumbar puncture, FDG-PET, and serum antibody testing for neural autoantibodies. The most commonly prescribed anti-seizure medications (ASMs) for LOE were levetiracetam (86.15%; $n = 56$), lacosamide (81.54%; $n = 53$), and lamotrigine (61.54%; $n = 40$).

Significance: These findings suggested that Italian epileptologists frequently evaluate patients with LOE during routine outpatient visits. LOEU is increasingly recognized as a distinct subtype of LOE that may warrant a targeted diagnostic approach due to the potential involvement of autoimmune and neurodegenerative mechanisms. There is a pressing need for focused cross-sectional or prospective multicenter studies to refine the diagnostic strategies for LOE, particularly for LOEU, and to enhance the characterization of its clinical and etiological features.

Plain Language Summary: After age 50, epilepsy rates rise, often linked to brain changes but sometimes with no clear cause (LOEU). We surveyed Italian epilepsy specialists and found that routine EEG and MRI are widely used, yet about 20% of cases require advanced tests to identify rare or autoimmune causes. Our findings will inform patient-focused diagnostic and treatment guidelines and underscore the need for standardized care pathways and further research in adult-onset epilepsy.

KEYWORDS

Alzheimer's disease, antiseizure medications, dementia, epilepsy, LOE

1 | INTRODUCTION

Epilepsy affects approximately 65 million individuals worldwide and ranks as the third most common neurological disorder among the elderly, following stroke and dementia.[1,2] The incidence of epilepsy notably increases after the age of 50, peaking in those over 75 years.[3–5] Older adults with epilepsy can be broadly classified into two subgroups: individuals with a longstanding history of seizures and those with late-onset epilepsy (LOE).[6] Although no universally accepted definition of LOE exists, epidemiological studies consistently report the highest incidence in the oldest age cohorts, with age thresholds ranging from 50 to 70 years.[7] In developed countries, including Italy, which has one of the world's oldest populations, the incidence of LOE rises significantly after age 59.[8]

The etiology of LOE is heterogeneous, with cerebrovascular diseases, traumatic brain injury, and brain tumors constituting the predominant causes.[9] While LOE is

Key points

- LOE incidence rises after age 59, a trend seen in Italy's aging population; LOE etiology is heterogeneous and lacks a uniform definition.
- LOEU cases form a distinct subgroup requiring tailored workup, focusing on neurodegenerative and autoimmune mechanisms.
- This cross-sectional survey of Italian epileptologists evaluates diagnostic and therapeutic approaches to LOE and LOEU.
- EEG and brain MRI are routinely used to exclude secondary causes; second-level tests target infections, autoimmunity, and degeneration.
- A pressing need exists for multicenter studies to refine LOE/LOEU diagnostic strategies and detail clinical and etiological features.

primarily associated with structural brain abnormalities, non-structural factors such as infections, autoimmune disorders, and neurodegenerative diseases also contribute to its pathogenesis.[10] Alzheimer's Disease (AD) and related dementias are estimated to account for 10%–20% of LOE cases.[9]

Remarkably, approximately 20% of LOE cases remain without an identifiable cause and are classified as late-onset epilepsy of unknown etiology (LOEU).[11] Emerging research suggests that individuals with LOEU frequently exhibit cerebral amyloid deposits, with amyloid-β (Aβ) accumulation correlating with an increased risk of cognitive decline following seizure onset.[12] Epilepsy itself is associated with a threefold increased risk of dementia, particularly when seizures begin later in life.[12–14]

Effective management of LOEU requires early neuropsychological evaluation and biomarker assessment to enable patient stratification. This approach facilitates personalized treatment strategies and may support enrollment in disease-modifying clinical trials, thereby improving management of this subgroup and highlighting the need for tailored therapeutic interventions.

In clinical practice, using a range of diagnostic tools is essential for accurately characterizing LOE, with the aim of optimizing treatment decisions and minimizing unnecessary procedures. This emphasis on individualized care aligns with the evolving paradigm in epilepsy management, which prioritizes patient-specific treatment efficacy.[10]

The present study seeks to elucidate the diagnostic and therapeutic approaches for LOE employed by Italian epileptologists. These efforts aim to clarify the diverse etiologies of adult-onset epilepsy and support the development of a patient-centered, adaptable management model to improve clinical outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design

Data were collected through a cross-sectional online survey targeting neurologists who are active members of *Lega Italiana contro l'Epilessia* (LICE), the Italian Chapter of the International League Against Epilepsy (ILAE). The survey was developed by the "Late-Onset Epilepsy Study Group" of LICE and consisted of six multiple-choice questions, designed based on current literature and expert consensus. Questions aimed to characterize the epidemiology of LOE and LOEU in Italy, and to explore the diagnostic tools most commonly used in clinical practice for these conditions. A detailed copy of the survey questions and response options is provided in the Appendix S1.

Survey participants were recruited during the 46th LICE National Congress (Naples, 7–9 June 2023) to ensure broad participation among LICE members. The survey link was also distributed via email to all attendees, and participants were given a 5-month window to complete the questionnaire. In cases where multiple responses were received from a single center, the respondents were asked to coordinate and submit one consolidated version.

2.2 | Identification of participant to the survey

All respondents were official members of LICE, a scientific society committed to the treatment and social integration of persons with epilepsy (PWE). LICE recently established a dedicated "Late-Onset Epilepsy Study Group" (https://www.lice.it/LICE_ita/gruppi/EPILESSIE_LATE-ONSET/componenti.php), which took the initiative to design and promote the current survey.

2.3 | Statistical analysis

Descriptive statistics were employed to summarize the collected data. Where appropriate, inferential statistical analyses were conducted to derive meaningful interpretations and identify significant trends.

3 | RESULTS

Neurologists from 65 distinct epilepsy centers across 19 of the 20 Italian regions participated in the study by completing the survey (Figure 1). Regarding the estimated annual number of individuals over the age of 55 newly diagnosed with LOE, 25 centers (38.46%) reported between 50 and 100 cases per year, 18 centers (27.69%) reported fewer than 50 cases, 13 centers (20%) reported between 100 and 200 cases, and 9 centers (13.85%) reported more than 200 cases annually.

The survey also investigated the diagnostic approaches adopted for LOE (Figure 2). All participating centers (100%; $n = 65$) reported performing routine awake EEG, while 92.31% ($n = 60$) routinely perform brain MRI, and 35.38% employ CT scans during initial evaluations. Neuropsychological testing is conducted in 35.38% ($n = 23$) of centers. Additionally, in over half of the centers (58.46%; $n = 38$), sleep-activated EEGs are utilized, with EEG following sleep deprivation being the most frequently used

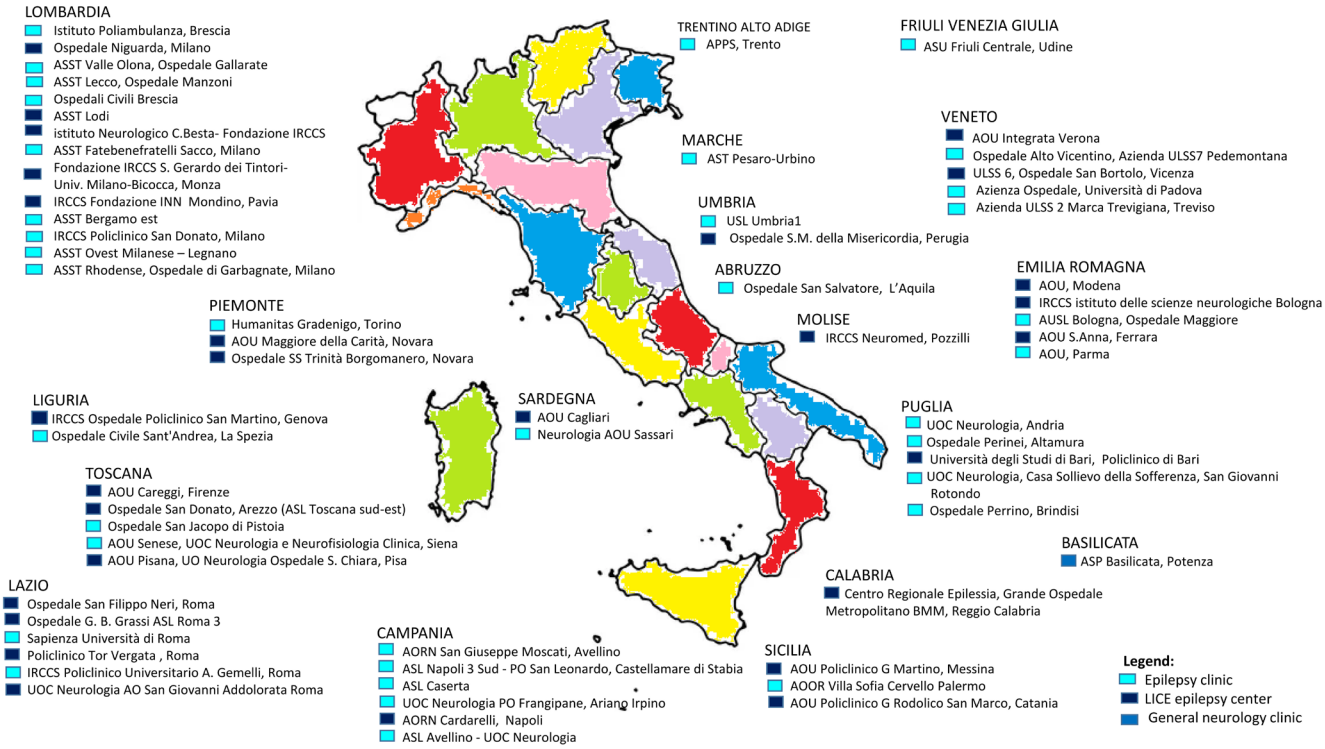

FIGURE 1 Epilepsy centers participating in the survey.

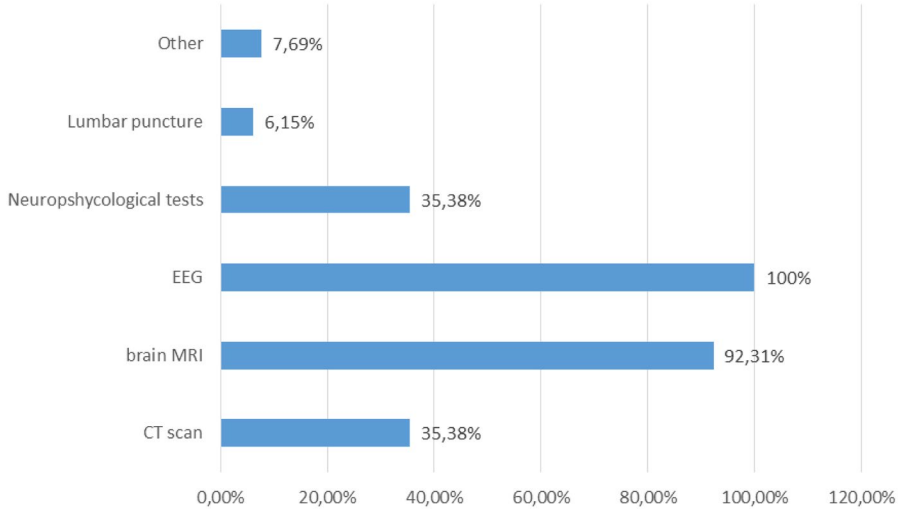

FIGURE 2 Answers to question 3 (multiple choice available): *Which kind of instrumental and laboratory diagnostic tools do you use in patients with LOE during the first evaluation at your center?*

modality (76%), followed by polysomnography (32%) and ambulatory EEG monitoring using portable devices (18%).

In the context of LOEU, the most frequently used diagnostic tools are MRI (76.92%; $n = 50$) and EEG (72.31%; $n = 47$) (Figure 3). If no clear etiology is identified following first-level investigations, patients are referred for more advanced, second-level diagnostic procedures before being classified as having LOEU. Specifically, in these cases, routine EEG is performed in 82.98% of centers, sleep-deprived EEG in 63.83%, polysomnography in 21.28%, and ambulatory EEG in 19.15%. Neuropsychological assessments are employed by 60% of centers, typically using a comprehensive battery of tests rather than a single screening tool. Moreover, over 30% of centers conduct advanced, third-level investigations such as lumbar puncture, 18F-fluorodeoxyglucose positron emission tomography

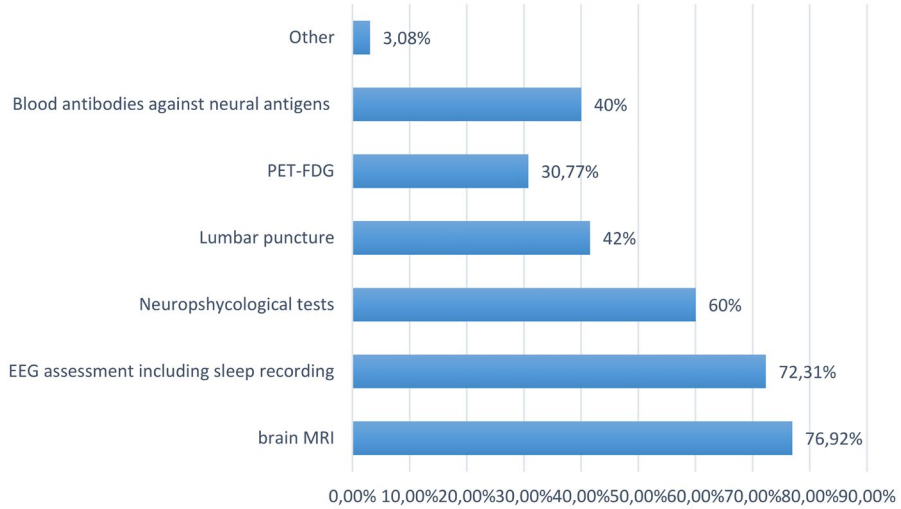

FIGURE 3 Answers to question 5 (multiple choice available): *In the case of patients with LOEU, do you use other diagnostic tools?*

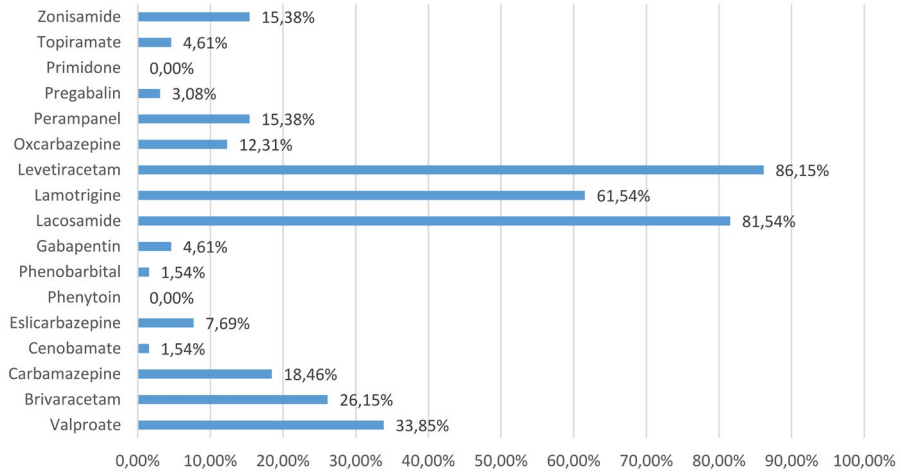

FIGURE 4 Answers to question 6 (multiple choice available): *Which ASMs are you used to adopt in patients with LOE?*

(PET-FDG), and serological testing for antibodies targeting neuronal antigens.

Regarding brain MRI, the most commonly used sequences include T2/FLAIR-weighted imaging (94%; $n = 47$), diffusion-weighted imaging (DWI) (86%; $n = 43$), and T1-weighted imaging with and without contrast enhancement (78%). In cerebrospinal fluid (CSF) analysis, more than 90% of clinicians test for antibodies against neuronal surface antigens, while 74% assess biomarkers of neurodegeneration, such as beta-amyloid and tau proteins.

The most frequently prescribed anti-seizure medications (ASMs) for LOE are levetiracetam (LEV) (86.15%; $n = 56$), lacosamide (LCS) (81.54%; $n = 53$), and lamotrigine (LTG) (61.54%; $n = 40$) (Figure 4). Among first-generation ASMs, valproate is the most commonly used (33.85%; $n = 22$).

4 | DISCUSSION

Epilepsy is increasingly common among the elderly, reflecting global improvements in living conditions and healthcare access, as well as the progressive aging of the population worldwide.[15,16] In the Rotterdam Study, which included individuals aged ≥55 years, the overall prevalence of active epilepsy was 9 per 1000, with age-related increases from 7 per 1000 in those aged 55–64 years to 12 per 1000 in those aged 85–94 years.[17] Notably, in high-income countries such as those in Europe and North America where the population is predominantly elderly, epilepsy with onset in later life has substantial clinical, social, and economic implications.[18]

Our findings indicate that LOE represents a significant clinical concern with high prevalence in Italy. More than 70% of neurologists who participated in the present

survey reported evaluating over 50 LOE cases annually, with over 25% assessing more than 100 cases per year. However, these data do not reflect national incidence rates, nor can they be extrapolated from the present survey.

In clinical practice, patients with LOE typically undergo thorough diagnostic evaluations to determine the etiology. Medical history, neuroimaging, EEG, and blood analyses generally allow for adequate etiological classification in most cases.[10] Among the 65 centers participating in the survey, all (100%) reported using routine awake EEG and 92.31% ($n = 60$) reported using brain MRI in the diagnostic workup. In contrast, head CT was used in only 35.38% ($n = 23$) of cases. This likely reflects the structure of the Italian National Health System, which provides full reimbursement for diagnostic procedures, including MRI, thereby facilitating detailed diagnostic evaluations.

Although CT remains useful when MRI is unavailable, the latter neuroradiological technique is clearly preferred due to its superior resolution and diagnostic value in epilepsy.[19] As recommended by the ILAE Neuroimaging Task Force,[20] many centers employ the HARNESS–MRI protocol, which includes isotropic 3D T1- and FLAIR-weighted images as well as high-resolution 2D submillimetric T2-weighted sequences. Some centers also perform MRI sequences designed to detect age-related pathologies associated with LOE. In particular, recent evidence has identified cerebral amyloid angiopathy (CAA) as a cause of LOE,[21,22] for which GRE and/or SWI sequences are essential to identify typical radiological features.

EEG was used in all centers for LOE diagnosis. In addition to routine analysis, more than half of the participating centers also employed sleep-activated EEG, predominantly via sleep deprivation, a method shown to significantly increase both the sensitivity and specificity of epilepsy diagnosis.[23,24] Among those using sleep-activated EEG, 32% also utilized polysomnography. This is especially relevant in patients with obstructive sleep apnea syndrome (OSAS), a condition that may predispose to seizures via intermittent hypoxia-induced oxidative stress and inflammation.[25] In these cases, polysomnography with oximetry is crucial for evaluating the severity of sleep apnea.

When first-level investigations fail to identify the cause of LOE, second-level assessments should be conducted to exclude non-structural causes, such as CNS infections, autoimmune encephalitis, and neurodegenerative diseases. Approximately 20% of LOE cases remain without a clear etiology and are classified as LOEU.[14]

In our survey, the most commonly used diagnostic tools for LOEU were MRI (76.92%; $n = 50$) and EEG (72.31%; $n = 47$). MRI protocols often included not only T1- and T2-weighted sequences sufficient to detect atrophy, but also DWI and GRE sequences (70% of centers). Regarding EEG, 82.98% used routine technique, 63.83% employed EEG after sleep deprivation, 21.28% utilized polysomnography, and 19.15% used ambulatory EEG. These modalities were not mutually exclusive.

EEG is a non-invasive, repeatable technique that, in addition to revealing epileptiform discharges, can provide insights into cortical network connections and longitudinal changes in brain activity potentially useful for monitoring progression toward dementia. There is growing evidence that EEG biomarkers may be clinically meaningful and correlated with the course of cognitive decline.[26–31] EEG at the time of epilepsy diagnosis may help stratify the risk of future cognitive deterioration in LOEU patients.

Seizures preceding cognitive symptoms may reflect the epileptogenic effects of amyloid-β, which accumulates in the brain years before the clinical onset of dementia.[32] These findings support the need for comprehensive LOEU evaluation including neuropsychological testing and CSF analysis to monitor cognitive trajectories.[10,33]

In line with this, more than half of the surveyed centers reported routinely conducting neuropsychological testing in patients with LOEU, most often employing a full battery including MMSE, RAVLT, Logical Memory, ROFC-del, TMT, FAB, SMDT, PM'47, MDB, and CDT. Furthermore, given the potential link between LOEU and neurodegenerative conditions, many centers also performed second-level tests such as lumbar puncture (42%) and FDG-PET (30%). Such thorough evaluations may detect Alzheimer's-related epilepsy even in patients without overt dementia. The combination of CSF biomarkers (e.g., amyloid-β, tau) and neurodegeneration indicators (e.g., MRI atrophy, PET hypometabolism) is considered the gold standard for diagnosing Alzheimer's disease and related conditions.[34]

CSF analysis is also critical for diagnosing antibody-mediated autoimmune encephalitis, in which seizures are often a presenting symptom. Some studies report that up to 23% of patients over age 60 with positive neural autoantibodies exhibit no MRI or CSF inflammatory changes.[35] In such cases, FDG-PET has shown greater sensitivity than MRI.[36–38] In our survey, more than 90% of clinicians reported testing CSF for antibodies against surface neural antigens. Early detection of antibody-mediated LOE is essential, as these patients often respond well to immunotherapy when treated in early stages.[39]

Despite advances in diagnostics, a significant proportion of LOE cases remain without an identified etiology.[10,13,14] Therefore, continued, research particularly large, targeted cohort studies is essential to expand our understanding of this evolving clinical entity.

Given the vulnerability of elderly patients, often with multiple comorbidities and polypharmacological treatments, the choice of ASM should be tailored to balance seizure control with tolerability and minimal side effects. Monotherapy is generally considered the optimal initial approach in older adults with uncomplicated epilepsy.[40] A recent systematic review and meta-analysis indicated that newer-generation ASMs—specifically LCS, LTG, and LEV—were the most effective monotherapies for achieving seizure freedom at 6 or 12 months, with no significant differences in efficacy among them.[41] Another systematic review focusing on patients with comorbid Alzheimer's disease reported similar seizure control among LEV, LTG, and phenobarbital (PB), though LEV was associated with cognitive improvement, while PB and LTG worsened cognitive function; PB also significantly worsened mood.[42,43] In accordance with these findings, our survey revealed that LEV, LCS, and LTG were by far the most commonly prescribed ASMs for LOE by Italian neurologists specialized in epilepsy.

4.1 | Limitations and strengths of the study

Surveys are a well-established method to explore knowledge, attitudes, and practices in healthcare settings.[44] In this context, the present study highlights both the relevance and the practical implementation of etiological assessment in LOE among Italian epileptologists. One key limitation is that, although the survey was distributed via the LICE mailing list, we do not have precise data about the total number of epileptologists who received the invitation or the overall response rate. Furthermore, while to our knowledge, there are no comparable published surveys on LOE from other countries or from general neurology outpatient clinics, it is reasonable to assume that specialized epileptologists such as those affiliated with LICE may be particularly attentive to the etiological workup of LOE patients. This likely accounts for their adoption of a state-of-the-art diagnostic approach, particularly in the stratification of cases of LOEU, and their frequent use of advanced diagnostic tools such as FDG-PET and CSF analysis, which may not be as routinely accessible or utilized in general neurology settings. However, the precise estimation of the actual number of LOE and LOEU cases in the general population, as well as the accurate quantification of diagnostic and therapeutic approaches applied in these patients, would require a retrospective, large-scale epidemiological study, an objective that extends beyond the scope of this survey.

5 | CONCLUSIONS

Although LOE remains a relatively underexplored condition and lacks a universally accepted definition, it is frequently encountered and managed by Italian neurologists specializing in epilepsy. Older adults with epilepsy constitute a heterogeneous population, and a comprehensive diagnostic approach is essential to evaluate all potential etiologies. Both EEG and brain MRI are widely employed by epileptologists to exclude secondary causes of LOE.

Among LOE cases, those of unknown etiology (LOEU) represent a distinct subgroup requiring a tailored diagnostic workup, with particular attention to possible neurodegenerative and autoimmune mechanisms. The Italian epilepsy network appears to have recognized the relevance of this association and is well equipped to pursue such diagnoses.

Now is the time for a coordinated effort, and the establishment of a dedicated Commission on the Study of LOE could play a pivotal role. This body could initiate a cross-sectional, multicenter study ideally in collaboration with geriatric specialists to better characterize the clinical features of LOE cases currently managed in epilepsy centers. In parallel, it could propose prospective studies that implement a standardized diagnostic pathway for LOE. Such an approach would be especially valuable for LOEU, for which a precise definition could be refined through preliminary data and ultimately serve as the foundation for a structured third-level diagnostic framework.

AUTHOR CONTRIBUTIONS

Elena Nardi Cesarini, Giovanni Falcicchio, Filippo Sean Giorgi, Jacopo C. DiFrancesco, and Cinzia Costa participated in study design, analyzed data, and wrote the first and final draft. Elena Nardi Cesarini and Giovanni Falcicchio performed statistical analysis. Elena Nardi Cesarini, Giovanni Falcicchio, Filippo Sean Giorgi, Jacopo C. DiFrancesco, Giovanni Assenza, Miriam Sciaccaluga, and Laura Librizzi collected data. Carlo Andrea Galimberti revised the manuscript for intellectual content.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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