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RESEARCH ARTICLE

Added value of advanced workup after the first seizure: A 7-year cohort study

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Abstract

Objective: This study was undertaken to establish whether advanced workup including long-term electroencephalography (LT-EEG) and brain magnetic resonance imaging (MRI) provides an additional yield for the diagnosis of new onset epilepsy (NOE) in patients presenting with a first seizure event (FSE).

Methods: In this population-based study, all adult (≥16 years) patients presenting with FSE in the emergency department (ED) between March 1, 2010 and March 1, 2017 were assessed. Patients with obvious nonepileptic or acute symptomatic seizures were excluded. Routine EEG, LT-EEG, brain computed tomography (CT), and brain MRI were performed as part of the initial workup. These examinations' sensitivity and specificity were calculated on the basis of the final diagnosis after 2 years, along with the added value of advanced workup (MRI and LT-EEG) over routine workup (routine EEG and CT).

Results: Of the 1010 patients presenting with FSE in the ED, a definite diagnosis of NOE was obtained for 501 patients (49.6%). Sensitivity of LT-EEG was higher than that of routine EEG (54.39% vs. 25.5%, $p < .001$). Similarly, sensitivity of MRI was higher than that of CT (67.98% vs. 54.72%, $p = .009$). Brain MRI showed epileptogenic lesions in an additional 32% compared to brain CT. If only MRI and LT-EEG were considered, five would have been incorrectly diagnosed as nonepileptic (5/100, 5%) compared to patients with routine EEG and MRI (25/100, 25%, $p = .0001$). In patients with all four examinations, advanced workup provided an overall additional yield of 50% compared to routine workup.

Significance: Our results demonstrate the remarkable added value of the advanced workup launched already in the ED for the diagnosis of NOE versus nonepileptic causes of seizure mimickers. Our findings suggest the benefit of first-seizure tracks or even units with overnight EEG, similar to stroke units, activated upon admission in the ED.

Pia De Stefano and Eric Ménétré contributed equally as first authors.

KEYWORDS
EEG, emergency department, first seizure, long-term EEG, MRI

1 | INTRODUCTION

Seizures are one of the most frequent neurological emergencies.[1] The diagnostic workup of a first seizure or seizurelike event (summarized as "first seizure event" [FSE]) is crucial to rapidly determine its origin, the best therapy, and prognosis. The importance of a precise diagnosis and an efficient therapy has been recognized in a number of prospective and retrospective studies, leading to evidence-based guidelines by the Academy of Neurology in 2007[2] and 2015.[3]

However, if the workup is confined to the emergency department (ED) and further examinations are left to the discretion of the general practitioner (GP) or an outside consulting neurologist, diagnosis may be delayed, not determined at all (i.e., if the patient does not show up at consultation), or even incorrect. Delay in diagnosis can lead to increased morbidity and mortality and has been recognized as a significant public health issue.[4] Correct diagnosis is particularly difficult to establish if seizures are characterized by nonmotor features, if the chronology of events is not properly reported, or if there are no witness reports. Distinguishing seizures from syncope or transient ischemic attacks is particularly challenging in the elderly given the similarities in clinical presentation in this patient group and the high frequency of old brain lesions in the elderly.[5] Diagnosis of psychogenic nonepileptic seizures might also be difficult in an emergency or outpatient setting and can lead to a significant delay in their identification.[6]

In most hospitals, workup at the ED includes a medical/neurological consultation, blood tests, brain computed tomography (CT), and routine electroencephalography (EEG). The full workup, however, requires a number of examinations, including overnight long-term EEG (LT-EEG) and magnetic resonance imaging (MRI), which are the most important techniques in this context, but not readily available in most EDs.

If routine EEG is normal or ambiguous but epilepsy is suspected, (LT)-EEG can detect interictal epileptiform discharges (IEDs) in 30% of those patients.[7,8]

The superiority of MRI over CT in the first seizure context has been shown in several studies, and it allows revealing epileptogenic lesions in approximately 25% of all patients.[9,10]

Acute symptomatic seizures need to be diagnosed and treated,[11] but not necessarily treated with antiseizure medication (ASM). In addition, several new syndromes have been described in the past 10–20 years that differ in prognosis from structural or genetic epilepsy. For example, posterior reversible encephalopathy syndrome was first reported in the 1990s,[12] and autoimmune limbic encephalitis in 2004,[13] both requiring specific treatment, such as immunomodulating or antihypertensive agents. Such underlying pathologies may be difficult to identify at the time of the first event, but become apparent with additional specific tests, requiring expertise in epileptology and general neurology. If misdiagnosed, these and other phenomena that "mimic" seizures may relapse, leading to potentially major complications in relation to the underlying disease.

Key Points

- Advanced workup (MRI and LT-EEG) provided an added value of 50% for the diagnosis of NOE in patients presenting with a first seizure
- Sensitivity of LT-EEG was higher than that of routine EEG (54.4% vs. 25.5%)
- Sensitivity of MRI was higher than that of CT, showing epileptogenic lesions in an additional 32%
- Our findings suggest the benefit of first-seizure tracks or even units with overnight EEG

In a previous prospective study, our group showed that a swift and comprehensive workup (including a consultation by an epileptologist in the ED, routine EEG or LT-EEG, MRI, and three follow-up consultations at 3 weeks, 3 months, and 12 months) more often led to a precise diagnosis of the index event than an unstructured workup (64% vs. 43%).[8]

In the present study, we took this a step further and investigated the sensibility and specificity of routine EEG, LT-EEG, brain CT, and brain MRI and the added value of advanced workup (MRI and LT-EEG) to diagnose new onset epilepsy (NOE).

2 | MATERIALS AND METHODS

2.1 | Patients

Based on the charts, we retrospectively included all patients aged ≥16 years who presented an FSE between

March 2010 and March 2017 and were admitted to the ED of the University Hospital of Geneva. We excluded patients with clear acute symptomatic seizures and patients with known epilepsy admitted to the ED for relapses of epileptic seizures (included if uninvestigated previous seizures), psychogenic events immediately identified in the ED by the neurologist and psychiatrist (e.g., prolonged hypermotor event with fluctuating semiology and intensity, forced eye closure), and other causes with clear non-neurological origin, for which no EEG was requested (e.g., ischemic heart attack). Personal and family history was carefully reviewed for each patient, including psychiatric and cardiac diseases and, if necessary, with the patient's family and friends.

The study was approved by the local ethics committee. The STROBE guidelines were followed to assure the quality of our study.[14]

The study was designed to determine the added value of advanced workup (LT-EEG and MRI) in patients with NOE. Because the University Hospital of Geneva is the only hospital with an emergency neurology service in the canton of Geneva (506 343 citizens in December 2020) and all citizens benefit from health care, this study is practically population-based. All patients included in the study were followed for at least 2 years, when the final diagnosis was established.

Definition of NOE was based on the International League Against Epilepsy (ILAE) criteria ([1] at least two unprovoked seizures occurring >24 h apart, [2] one unprovoked seizure and a probability of further seizures of at least 60% over the next 10 years, [3] diagnosis of an epilepsy syndrome).[15] The second criterion was defined as the presence of a first unprovoked seizure and either an epileptiform abnormality on EEG or an abnormal brain imaging (with an epileptogenic lesion), both conditions led to >60% risk of seizure recurrence, in line with previous studies.[16]

2.2 | Workup

In the ED of the University Hospital of Geneva, each patient with FSE (and suspicion of epilepsy) receives a neurological consultation. A routine EEG (19 channel EEG, 20–30-min duration, including photic stimulation and hyperventilation) is prescribed and carried out as soon as possible, including weekends and holidays. Patients receive an electrocardiogram (EKG) and basic laboratory tests; most patients also receive brain CT. If CT and routine EEG are unrevealing, or if the CT shows a lesion of unclear nature, a 3-T MRI is performed, using established epilepsy imaging protocols,[9] interpreted by a neuroradiologist.

We consider tumor, old cortical strokes, chronic subdural hematomas, and cavernomas as relevant cerebral lesions on CT and MRI, allowing the clinician to diagnose epilepsy with high certainty if the semiology is concordant. For patients with suspicious semiology but negative routine EEG, LT-EEG is requested and performed as soon as possible. In our institution, LT-EEG is an overnight EEG recording lasting on average 18 h.

We considered routine workup as neurological status with patient history, routine EEG, and CT as soon as possible, but at our center usually within 48 h. Advanced workup included LT-EEG and MRI as soon as possible after the event. All EEGs, including LT-EEG, were always coupled with video footage.

If a psychogenic origin is suspected, a psychiatric consultation is organized in the ED, during the LT-EEG, or shortly thereafter. A psychogenic diagnosis is retained only if there are a positive psychiatric diagnosis and relevant psychological circumstances regarding the event. Overnight LT-EEG also allows EKG monitoring during various stages of wake and sleep and was carefully reviewed together with the EEG. If a cardiac origin was suspected, we requested Holter EKG for 24 h, R-Test for 1 week, a tilt test, or in some cases, a cardiac monitor.

Routine EEG as well as LT-EEG were examined for IEDs, namely, spikes, spike-waves, and sharp-slow wave complexes, as well as monomorphic focal delta rhythm (i.e., lateralized rhythmic delta activity [LRDA][17]) or ictal pattern. If the epileptiform nature of the EEG pattern was not clear, this EEG was discussed among the local senior EEG experts (P.D.S., S.V., F.P., P.M., M.S.). In the case that NOE was diagnosed, ASM was given. If a relapse occurred in patients with unclear diagnosis, workup was repeated.

2.3 | Statistics

Data analysis and statistics were performed using R software.[18] Proportion differences were compared using chi-squared tests. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio of each examination. Each measure was calculated with 95% confidence intervals. The yield of one workup configuration or examination over another was estimated by the combined yield, that is, the sensitivity difference between two examinations. A workup was considered positive if either an IED or epileptogenic lesion was noted. To calculate the differences in sensitivity between advanced and routine examinations, the number of true positive and true negative results were compared between examinations using a McNemar chi-squared test.

3 | RESULTS

We included 1010 patients (441 women, 43.7%), with a mean age of 53 years (SD = 22), ranging from 16 to 98. Seventy-seven patients (7.6%) had a history of uninvestigated similar events. Among 750 patients for whom it was possible to determine the time to the final diagnosis, most patients were diagnosed already in the ED (502/750, 66.9%); 531 (531/750, 70.8%) within 7 days; 592 (592/750, 78.9%) within 1 month; 660 (660/750, 88%) within 3 months, and 705 (705/750, 94%) within 6 months.

Almost half of the patients were diagnosed with NOE (501/1010, 49.6%). Forty-one of 501 suffered from at least two events, that is, they had been diagnosed following the first ILAE criterion; 460 of 501 were diagnosed on the basis of the second ILAE criterion. None of our patients fulfilled the third ILAE criterion.

Figure 1 summarizes the distribution of the 1010 patients among the different diagnoses. In 99 patients, the diagnosis could not be determined (9.8%). Among these patients, 14 patients received MRI, routine EEG, and LT-EEG, but the diagnosis remained unclear. The remaining 85 patients were lost to follow-up.

Detailed final diagnosis of 127 patients with "other" causes, but no NOE, are presented in Table 1.

3.1 | Routine EEG

Among patients with a routine EEG, 134 of 993 (13.5%) showed epileptogenic EEG abnormalities. In 316 of 993 (31.8%), the EEG showed only unspecific abnormalities, and in 543 of 993 (54.7%) patients, the routine EEG was completely normal. Routine EEG showed IEDs in 127 of 501 patients with NOE (25.3%) who underwent this examination. IEDs were noted in seven patients with nonepileptic conditions. In five of them, the origin of the observed epileptic discharges was attributed to

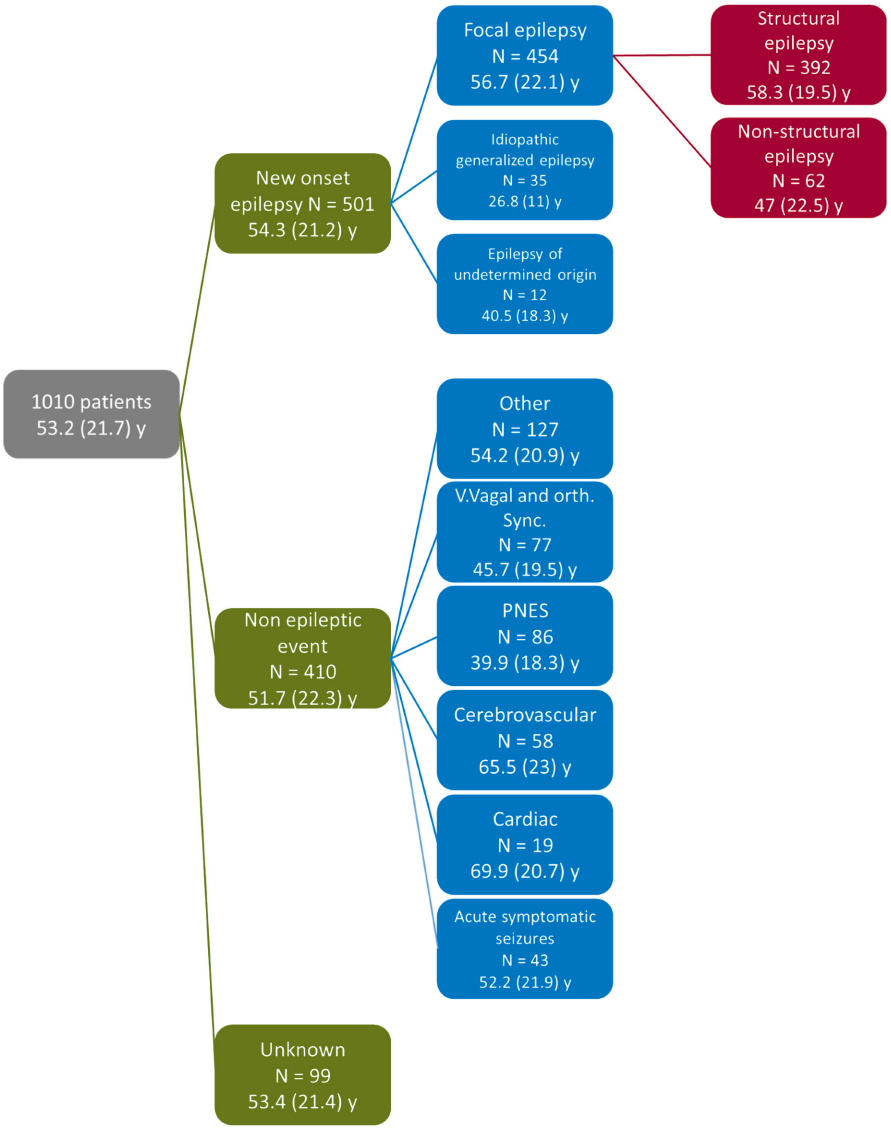

FIGURE 1 Final diagnosis after 2 years. The absolute numbers, mean age, and SD (in parentheses) are shown in each bullet for each diagnostic category. orth., orthostatic; PNES, psychogenic nonepileptic seizures; Sync., syncope; V.Vagal, vasovagal.

TABLE 1 Causes of nonepileptic events ($N = 127$).

Diagnosis	*n*
Migraine and other cephalic pain syndromes with neurological deficits	21
Delirium	17
Transient global amnesia	17
Impaired consciousness due to internal complications (cardiac arrest, hypoglycemia, respiratory failure, hyperglycemia, adrenal insufficiency)	13
Parasomnia and other sleep disorders	10
Multifactorial (all nonepileptic causes)	8
Medication side effects (e.g., neuroleptic medication)	7
Intoxication	5
Intermittent dysesthesia of peripheral origin	4
Dumping syndrome	4
Brainstem migraine	4
Cognitive impairment of presumably abrupt onset	3
Psychiatric disorders (new onset psychosis, intermittent hallucination)	3
CNS tumor-related symptoms (postoperative edema, complications of shunt)	3
Asymmetric tremor (alcohol withdrawal, multiple sclerosis, Parkinson syndrome)	3
Vertigo and inner ear dysfunction	1
Posterior reversible encephalopathy syndrome	1
Denutrition	1
Esophageal obstruction	1
Visual symptoms due to intermittent ocular pathology	1

Abbreviation: CNS, central nervous system.

psychotropic medication (i.e., antipsychotics and high-dose antidepressants), which disappeared with drug decrease or change of medication. Regarding the remaining two other cases, their EEG showed rare sharp waves in patients later diagnosed with psychogenic nonepileptic and acute symptomatic seizures, respectively. Thus, false positive IEDs in the routine EEG were 1.7% (7/410) considering all patients without NOE, or .5% (2/410) of cases if the medication effect is taken into account in the interpretation of findings.

In 350 of 501 (69.9%), the routine EEG was done within 24 h. If the routine EEG was obtained within 24 h, the chances of identifying IEDs in patients with NOE were significantly higher compared with EEGs done later (within 24 h: 99/350, 28.3%; >24 h: 28/151, 18.5%; $p = .021$; regarding all patients: 127/501 vs. 7/410, $p < .001$; Figure 2). The EEG median time period when performed later (>24 h) was 6 days.

3.2 | Long-term EEG

In 238 patients, LT-EEG was scheduled as part of their workup. Of those with a final diagnosis of NOE and normal or unspecific routine EEG and who underwent an LT-EEG ($n = 87$), 40 had discharges in the LT-EEG, resulting in an additional yield of 46%. In 29 patients, routine EEG showed IEDs but LT-EEG was scheduled due to incertainty of underlying epilepsy syndrome. IEDs in LT-EEG were detected in two of 158 cases of nonepileptic events and psychotropic medication, including one patient with an acute symptomatic seizure and another patient who experienced a transient ischemic attack, corresponding to two of 238 (.8%) false positive findings in patients without NOE.

LT-EEG was carried out as early as possible after the index event. Overall, 44 patients underwent LT-EEG during the first week, and the remaining patients ($n = 194$) after the first week or later. There was a strong trend of a higher chance of capturing IEDs during the first 7 days compared to later, but this did not reach significance ($p = .083$; Figure 2).

3.3 | Computed tomography

Eight hundred of 1010 (79.2%) underwent a brain CT. Diagnosis of NOE with the CT alone was obtained in 241 patients (241/800, 30.1%), leading to the introduction of ASM. In 559 patients, the CT was unrevealing or otherwise not contributing, and in 62 patients no CT was performed because other elements identified in the patient's history and

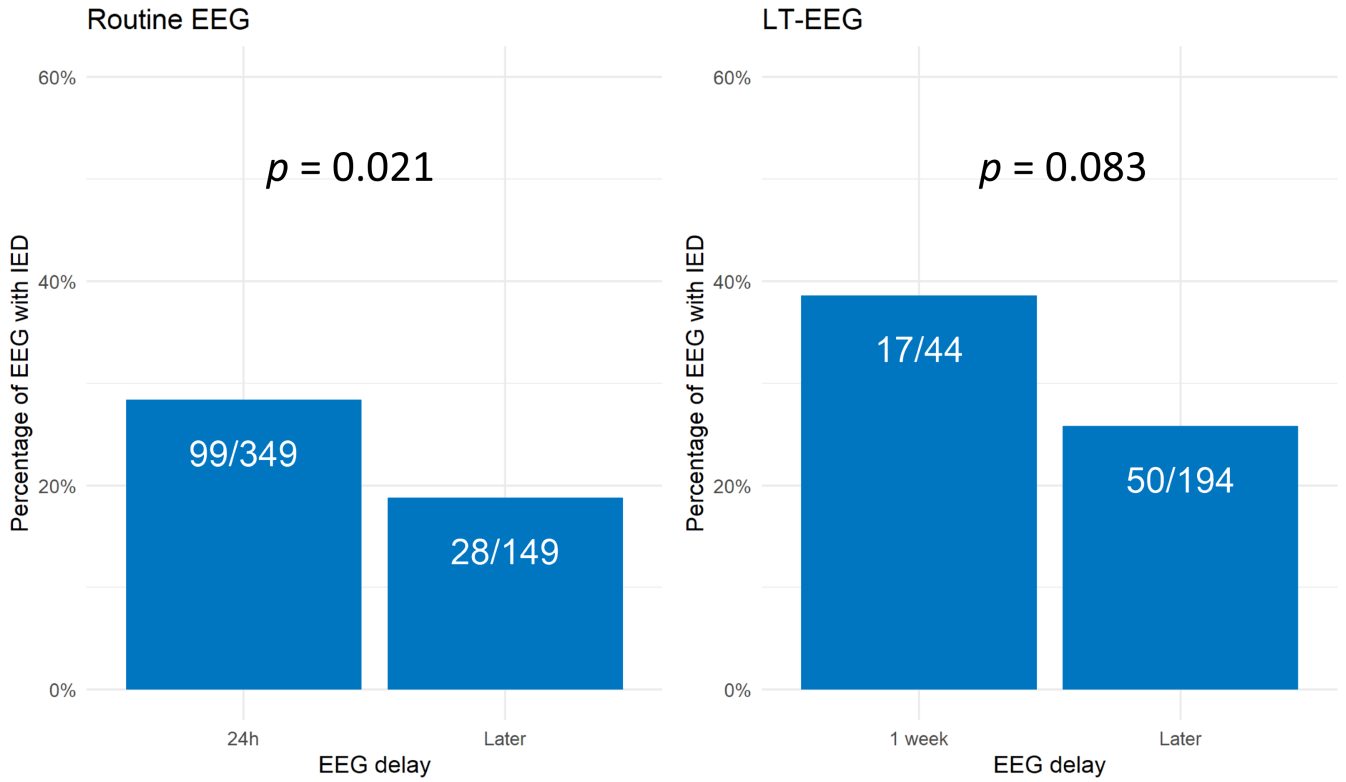

FIGURE 2 Left: Proportion of patients with new onset epilepsy showing interictal epileptiform discharges (IEDs) on routine electroencephalography (EEG) if carried out within the first 24 h versus >24 h (Later; $p = .021$). Right: Proportion of patients showing IEDs in the long-term EEG (LT-EEG) within the first week versus >1 week (Later; $p = .083$).

physical examination were sufficient for establishing a final diagnosis (e.g., generalized IEDs in the EEG and history of myoclonic jerks in the morning; asystole during the routine EKG, severe hypoglycemia). In cases where there was doubt on a focal seizure or EEG component, or other elements indicating focal dysfunction, or a complication of the event (e.g., skull fracture), CT imaging was added.

3.4 | Magnetic resonance imaging

This examination was ordered for 650 patients (64.3%), including 148 patients without prior CT. Brain lesions indicating the introduction of an ASM were identified in 320 patients (49.2%, 320/650). In NOE patients, MRI showed epileptogenic lesions in an additional 32% when the CT was normal (33/103 NOE patients with a normal CT) (Table 2).

3.5 | Advanced workup

In 71.1% (292/411) of NOE patients, definite diagnosis could not be obtained by a routine workup alone and needed LT-EEG and/or MRI, that is, an advanced workup (Figure 3).

Among 199 (100 NOE) patients with all three examinations (routine EEG, LT-EEG, and MRI), if only routine EEG and MRI were taken into account, 25 patients with IEDs on their LT-EEG would have been missed (25/100, 25%). If only MRI and LT-EEG were considered, five would have been incorrectly diagnosed as nonepileptic (5/100, 5%, $p = .0001$). In these cases, the routine EEG showed IEDs, but not the LT-EEG, which was requested at a later time point to better differentiate between focal and generalized epilepsy and patients received medication in the meantime.

Seventy-five patients received all four examinations (routine EEG, LT-EEG, CT, MRI); sensitivity was highest with the combination of MRI and LT-EEG (advanced workup; 57/75, 76%) compared to routine EEG and CT (routine workup; 28/75, 37.3%, $p < .001$; Table 3).

4 | DISCUSSION

This retrospective study of 1010 adult patients included 49.4% patients with NOE, 40.6% epilepsy mimickers, and 9.8% events of unknown origin, despite a comprehensive workup of most of the patients.

Sensitivity of LT-EEG was higher than that of routine EEG (54.39% vs. 25.5%). Similarly, sensitivity of MRI was

TABLE 2 Sensitivity, specificity, PPV, NPV, accuracy, and OR in patients with NOE versus those with other diagnoses for routine EEG, LT-EEG, CT and MRI.

	Sensitivity (lower–upper 95% CI)	Specificity (lower–upper 95% CI)	PPV (lower–upper 95% CI)	NPV (lower–upper 95% CI)	OR (lower–upper 95% CI)
Routine EEG [IED vs. unspecific abnormalities + normal]	25.5 (21.7–29.33)	98.49 (97.3–99.7)	95.49 (92–99)	51.38 (47.8–54.9)	22.36 (9.7–51.3)
LT-EEG [IED vs. unspecific abnormalities + normal]	54.39 (45.24–63.53)	96.23 (92.6–99.85)	93.94 (88.2–99.7)	66.23 (58.8–73.7)	30.4 (10.5–88.2)
MRI [epileptogenic lesion vs. intermediate abnormal + normal]	67.98 (63.13–72.82)	71.2 (65.59–76.81)	77.07 (72.4–81.7)	60.96 (55.4–66.6)	5.25 (3.7–7.5)
CT [epileptogenic lesion vs. intermediate abnormal + normal]	54.72 (49.92–59.52)	91.8 (88.72–94.88)	90.4 (86.3–93.7)	59.96 (55.5–64.4)	13.54 (8.6–21.3)

Abbreviations: CI, confidence interval; CT, computed tomography; EEG, electroencephalography; IED, interictal epileptiform discharge; LT-EEG, long-term EEG; MRI, magnetic resonance imaging; NOE, new onset epilepsy; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

higher than that of CT (67.98% vs. 54.72%). Overall, specificity was higher in EEG (routine EEG 98.49%, LT-EEG 96.23%) than in imaging examinations (CT 91.8%, MRI 71.2%). In patients with NOE, LT-EEG ($n = 80$) resulted in an additional yield of 46% compared to routine EEG and brain MRI showed epileptogenic lesions in an additional 32% compared to brain CT. Taking our findings together, we provide evidence of the added value of an advanced workup launched already in the ED for the diagnosis of NOE in a patient presenting with an FSE.

The yield of early routine EEG has been demonstrated in a mixed pediatric and adult population including children as young as 5 years.[19] In this study, IEDs were noted in 51% if the EEG was carried out within 24 h, compared to 34% if EEG was done later. The number of early positive examinations was lower in the present study (25.3%), most likely due to the absence of young children, in whom the likelihood to capture IEDs is overall higher.[20] However, the additional yield of early routine EEG could be also confirmed in this mostly adult population.

LT-EEG provided an impressive additional yield of 47% over routine EEG, which is higher than in most previous studies.[7,8] This may be because in most studies, EEG after sleep withdrawal was organized instead of a whole night EEG. IED rates of focal epilepsies usually show an important increase during stages 3 and 4 of slow wave sleep,[21] which are more easily obtained with a full night of sleep compared to sleep recordings during the day with a stressed patient in a busy EEG laboratory, despite maximal sound protection. Moreover, monomorphic delta activity like temporal LRDA was not considered as epileptiform abnormality in older studies, leading to lower incidence of IEDs.

A recurring clinical question is that of the sensitivity and specificity of routine EEG studies. There were 25 false negative and seven false positive routine EEGs. Five of the seven false positive cases were on clozapine. This drug has been described in association with seizures[22,23] and IEDs in the EEG,[24] underlining the need for careful review of the medication history when interpreting the EEG. In the other two cases, IEDs were rare and of unclear value, and not confirmed in the LT-EEG.

In LT-EEG, the rates of false positive and false negative EEG are markedly lower. If taken as an isolated examination, the yield of LT-EEG appears to be higher than that of routine EEG. Only five false negative and two false positive LT-EEGs were identified, and the performance of LT-EEG improved if combined with MRI.

MRI was associated with decreased odds compared to CT and a small confidence interval in the identification of epileptogenic lesions. However, the exact nature of the lesion is better determined by MRI. Thus, the

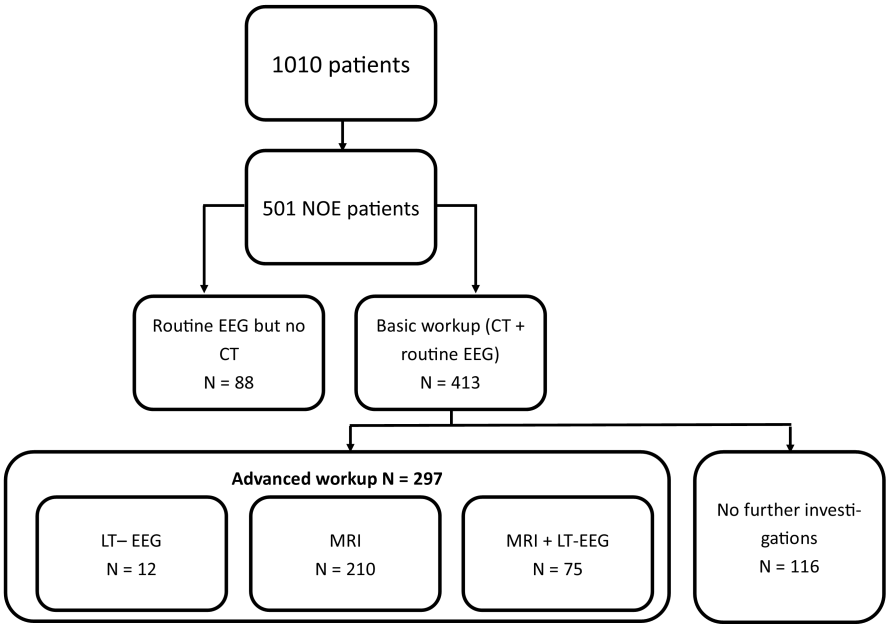

FIGURE 3 Workup for new onset epilepsy (NOE) patients. CT, computed tomography; EEG, electroencephalography; LT-EEG, long-term EEG; MRI, magnetic resonance imaging.

	LT-EEG	Routine EEG
MRI, *n* (%)	Advanced workup: 57/75 (76)	42/75 (56)
CT, *n* (%)	48/75 (64)	Routine workup: 28/75 (37.3)

Abbreviations: CT, computed tomography; EEG, electroencephalography; LT-EEG, long-term EEG; MRI, magnetic resonance imaging.

TABLE 3 Yield of the different combinations of examinations in 75 patients with NOE who underwent all four examinations (routine EEG, LT-EEG, MRI, CT).

introduction of an ASM following MRI was reported in 49.2% of patients versus 30.1% following CT, corresponding to an increased yield of 32% in NOE patients. This compares favorably with the results from other studies and supports the notion of the superiority of MRI over CT in the FSE context for the detection of the epileptogenic lesion.[9,10]

Taking our observations together, an advanced workup should be launched in the ED as soon as possible by or in close collaboration with the attending neurologist.

Our study was not designed to evaluate the yield of EEG and MRI in nonepileptic conditions. Nevertheless, our results suggest that NOE could be ruled out safely in >90% of our nonepileptic patients with LT-EEG and MRI. For the diagnosis of nonepileptic conditions, CT/MRI and routine EEG alone are insufficient, given the low yield of EEG for any other disease than epilepsy and the presence of nonspecific or old lesions with unclear relevance for the FSE.

Psychogenic and cardiovascular conditions are the most frequent seizure mimickers. The diagnosis of psychogenic nonepileptic seizures can be delayed for several years, if the initial diagnostic procedure is incomplete.[25] In two prospective studies, the benefit of specialized psychological intervention by first seizure clinics have been underlined.[26,27] LT-EEG appears particularly useful not only to search for IEDs but also to capture habitual spells on video-EEG recording. In this regard, the use of videophone should be encouraged as it helps to diagnose epileptic versus nonepileptic seizures.[28,29]

The diagnostic process of cardiac syncope is often long and divided between the GP and the cardiologist, usually outside the hospital, and may be complicated for elderly patients with reduced mobility. The semiology might be very similar to seizures or transient ischemic attacks,[30,31] and history-taking alone is often not sufficient. Holter EKG has a low diagnostic yield, and most authorities in the field underline that the early use of implantable EKG may be more cost-effective for workup of unclear neurological deficits.[32,33] Future studies are mandatory to determine the yield of immediate care starting in the ED and optimal diagnostic approach also for nonepileptic FSE conditions.

We did not investigate relapse rate after the first seizure, in contrast to previous studies focusing on seizure relapse before or after treatment introduction[16,34]; however, we followed the current ILAE criteria for the diagnosis of epilepsy, which those studies inspired. They demonstrated that in the absence of immediate treatment the risk of seizure recurrence after a first unprovoked seizure at 8 years is already 52%[34] and that abnormal epileptiform EEG, abnormal neurological examination, and seizure etiology

are the strongest predictors that put the patient at higher risk for seizure recurrence.[16,35]

4.1 | Limitations

Our study has several limitations.

With its retrospective design, we included only those patients with nonepileptic conditions who presented mimickers of focal or generalized seizures, necessitating neurological workup. Thus, the number of false negative and false positive results may be under- or overestimated with respect to the true frequency of IEDs in routine and LT-EEG in patients with nonepileptic conditions. However, this reflects the habitual clinical scenario, that is, scheduling specialized examinations only for unclear cases. Our study population contained 10% patients with FSE of unclear origin, that is, the diagnosis could not be determined between an "epileptic unprovoked seizure" and a "nonepileptic event." It is not excluded that we missed patients with NOE. Witness reports of varying semiology and negative EEG and MRI examinations indicated likely absence of NOE. Because we required a Diagnostic and Statistical Manual of Mental Disorders, 5th edition diagnosis of psychopathology to diagnose psychogenic nonepileptic seizures, we adopted a conservative approach and labeled these patients as "unknown." Thus, our calculated rates reflect realistic numbers of false positive and false negative findings in patients with NOE and nonepileptic conditions, imitating NOE.

Another aspect to consider is the interrater variability when interpreting the EEG, in particular in those countries where EEG education is not uniform and/or where clinical EEGs are typically read by neurologists without postresidency training in EEG/epilepsy.[36–38] However, all EEGs were reviewed by at least one certified EEG reader, all of whom have regular exposure to emergency EEGs, thus minimizing interrater variability.

5 | CONCLUSIONS

The results of this retrospective study of 1010 patients showed that an advanced workup combining MRI and LT-EEG outperformed basic workup with CT/routine EEG, providing an additional yield of 50%. We therefore consider MRI together with prolonged overnight video-EEG monitoring upon the patient's admission to provide the optimal combination to rapidly diagnose NOE and exclude seizure mimickers with high sensitivity and specificity. This advanced workup combines the yield of LT-EEG and high-resolution imaging together with patient monitoring and minimizes the risk of event-related morbidity and mortality including sudden unexplained death in epilepsy, which is already two to three times elevated after the first event.[39]

Although sleep withdrawal is an established option to obtain sleep EEGs, LT-EEG allows the recording of all sleep stages including morning EEG, which is useful for the diagnosis of idiopathic generalized epilepsy syndromes. Thus, overnight LT-EEG has an excellent diagnostic yield, and should be integrated into specialized first seizure care units.[40] In addition, 5%–18% of the patients present a relapse while still in the ED.[41,42]

Based on our results, we propose the creation of first seizure units allowing brief hospitalizations or, if this is not possible, first-seizure networks (i.e., dedicated neurophysiologists, neurologists, neuroradiologists, etc. working in collaboration on an outpatient level), active upon patient admission to the ED, similar to stroke units and centers, which have shown excellent yield in terms of morbidity and mortality.[40] This could avoid unnecessary delay in diagnosis.[4] It is of note that a recent retrospective cohort study showed a significant reduction of premature mortality in patients with epilepsy who were exposed to specialist care.[43]

We are aware that many hospitals and EDs do not have access to timely routine EEGs, and an even larger number have only delayed access to LT-EEG or MRI for FSE, but based on our findings and our experience, we strongly encourage identifying resources to make such diagnostic examinations available in the acute setting.

Although mortality and morbidity are quite different between stroke and FSE, the latter affects younger patients with a longer life expectancy. If early diagnosis is not established and treatment is not given, recurrent events may translate to high direct and indirect costs. Proper advanced workup and care in the acute phase may well be a cost-effective maneuver, but this warrants future research and investigation, as well as the controversial question of whether immediate treatment introduction in all patients after the first seizure is appropriate and effective.

AUTHOR CONTRIBUTIONS

Pia De Stefano acquired and interpreted the data, planned and designed the study, and drafted the manuscript. Eric Ménétré planned and designed the study, acquired and interpreted the data, performed the statistical analyses, and drafted part of the manuscript. Patrick Stancu acquired data and revised the manuscript. Pierre Mégevand, Maria Isabelle Vargas, Andreas Kleinschmidt, Serge Vulliémoz and Roland Wiest revised the manuscript and contributed to the inaugural draft. Sandor Beniczky and Fabienne Picard contributed to

designing the study, revised the manuscript, and contributed to the inaugural draft. Margitta Seeck planned and designed the study, acquired and interpreted the data, revised the manuscript, and substantially contributed to the inaugural draft. All authors approved the final submitted version.

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CONFLICT OF INTEREST STATEMENT

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