Standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders: an EAN, ESRS and ILAE-Europe consensus review

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Background and purpose: Some epilepsy syndromes (sleep-related epilepsies, SREs) have a strong link with sleep. Comorbid sleep disorders are common in patients with SRE and can exert a negative impact on seizure control and quality of life. Our purpose was to define the standard procedures for the diagnostic pathway of patients with possible SRE (scenario 1) and the general management of patients with SRE and comorbidity with sleep disorders (scenario 2).

Methods: The project was conducted under the auspices of the European Academy of Neurology, the European Sleep Research Society and the International League Against Epilepsy Europe. The framework entailed the following phases: conception of the clinical scenarios; literature review; statements regarding the standard procedures. For the literature search a stepwise approach starting from systematic reviews to primary studies was applied. Published studies were identified from the National Library of Medicine's MEDLINE database and Cochrane Library.

Results: Scenario 1: Despite a low quality of evidence, recommendations on anamnestic evaluation and tools for capturing the event at home or in the laboratory are provided for specific SREs. Scenario 2: Early diagnosis and treatment of sleep disorders (especially respiratory disorders) in patients with SRE are likely to be beneficial for seizure control.

Conclusions: Definitive procedures for evaluating patients with SRE are lacking. Advice is provided that could be of help for standardizing and

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improving the diagnostic approach of specific SREs. The importance of identifying and treating specific sleep disorders for the management and outcome of patients with SRE is underlined.

Introduction

Epilepsy and sleep have a reciprocal relationship. Sleep, sleep deprivation and sleep disorders may affect epilepsy, facilitating seizure occurrence; in turn seizures during sleep, drugs and interictal epileptic activity may fragment sleep, worsening seizures in a vicious circle, and interfere with its restorative and neuroplastic functions [1–6]. Seizures originating from different brain networks have a non-random distribution within the 24-h rhythm and tend to occur in different diurnal patterns [7–9]. Although patients with seizures during sleep may also have daytime seizures, sleep-related hypermotor epilepsy (SHE) [10] and other epilepsy syndromes are characterized by seizures nearly exclusively arising from sleep or shortly after awakening, or are characterized by an extreme potentiation of epileptiform activity during sleep. These epilepsy syndromes are defined under the term sleep-related epilepsies (SREs) [6,11,12]. Several clinical studies have shown that the presence of a comorbid sleep disorder is common in these patients, with a potentially negative impact on seizure control as well as reducing the quality of life [4,13–19].

There are no standard criteria regarding the procedures needed to investigate these epileptic conditions and patients with a suspicion of one of these disorders may undergo different, and potentially inappropriate, diagnostic tests across laboratories in Europe.

Objectives

The aim of the paper is to define the standard procedures for the diagnostic pathway of patients with possible SRE and the management of patients with SRE and comorbidity with sleep disorders. Our comorbidity analysis is focused on sleep-disordered breathing (SDB), insomnia and restless leg syndrome (RLS) as they represent the most common sleep disorders. Parasomnias are not considered in this document, as they deserve a specific analysis particularly relating to differential diagnoses.

The target audience of the paper is healthcare professionals who have contact with, or make decisions concerning the care of, patients with SRE. These standardized procedures cover care in primary, secondary and tertiary services.

Methods

This consensus review was conducted under the auspices of the European Academy of Neurology (EAN), the European Sleep Research Society (ESRS) and the International League Against Epilepsy (ILAE) Europe. A working group of epileptologists and sleep experts, together with a methodological support, was formed after consultation of the three societies. According to the EAN documents for the production of guidelines [20,21], the group adapted the recommendations in order to produce an 'EAN consensus review' [21]. The protocol was approved by the EAN in January 2017. Draft statements were discussed during a meeting in Bologna in April 2018.

The conceptual framework of the review entailed the following phases: design of the clinical scenarios; literature review; statements regarding the standard procedures for the diagnostic pathways.

Experts devised the diagnostic pathway for sleep-related paroxysmal clinical and/or neurophysiological manifestations suggestive of SRE (scenario 1) and in the case of suspicion of sleep disorder comorbidity in patients with SRE (scenario 2).

Each scenario was split into basic questions using the population–intervention–comparator–outcome (PICO) structure, addressing the diagnostic accuracy of each diagnostic step, or the effectiveness of the management of sleep comorbidity in patients with SRE.

The target population consisted of patients of any age with suspected or diagnosed SRE (see below). The literature search was performed in May 2017 and updated in June 2018 and June 2020 (Appendix S1) applying a stepwise hierarchical approach: at first, inclusion of systematic reviews; in the absence of systematic reviews, inclusion of primary studies. Published studies were identified from the National Library of Medicine's MEDLINE database and Cochrane Library. For the qualitative aspects of the scenarios (flow of patients, professional and technical features, theoretical issues) a comprehensive literature review was performed by experts. In the case of scenarios possibly referring to more general situations (e.g. diagnosis and treatment of comorbidity), experts integrated knowledge from evidence-based clinical practice guidelines. The quality of evidence of primary

studies was graded according to the Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the American Academy of Neurology [22], from class I (highest quality) to class IV (lowest quality). For each PICO, a summary reporting results and quality of studies was drafted by working groups. Then statements regarding the procedures for both scenarios were developed and synthesized into diagnostic pathways, through iterations and critiques with differences resolved through consensus. Questions with limited or no evidence were evaluated to identify research gaps and develop recommendations for future research.

Definition of sleep-related epilepsies

Under the term SREs, three main categories of epilepsies or epilepsy syndromes were included that share an innate robust relationship with sleep, as they are characterized by (i) seizures exclusively or almost exclusively from sleep (sleep-associated epilepsies); (ii) consistent extreme potentiation of electroencephalography (EEG) epileptiform activity during sleep (sleep-accentuated epilepsies); (iii) seizures typically occurring in the period after awakening from sleep (awakening epilepsies).

Sleep-associated epilepsies

- Sleep-related hypermotor epilepsy (SHE), formerly known as nocturnal frontal lobe epilepsy, is characterized by seizures that arise from sleep and manifest as complex motor behaviours or sustained dystonic posturing [10]. The prevalence of SHE is 1.8–1.9 per 100 000 in the adult population [23]; its aetiology is genetic, structural or in most cases unknown, and long-term prognosis is unfavourable [24].
- Epilepsy with centrotemporal spikes (ECTS) and Panayiotopoulos syndrome (PS) are the most frequent syndromes of idiopathic/self-limited focal epilepsy in children, representing up to 20% and 13% of childhood epilepsies respectively [25,26]. In both, seizures occur mainly during non-rapid-eye-movement (NREM) sleep [27–29] and typically remit before or at adolescence.

Sleep-accentuated epilepsies

- Electrical status epilepticus in sleep (ESES) is a developmental epileptic encephalopathy with a characteristic EEG activation upon sleep onset that persists throughout NREM sleep [30,31]. Seizure evolution is usually benign, but neuropsychological and behavioural disturbances may be pronounced [6,32,33]. Cortical and thalamic lesions are present in almost half of the patients [34]. A genetic mutation (GRIN2A), found in a subgroup of patients with ESES, ECTS and Landau–Kleffner syndrome (LKS), suggests a continuum between these disorders [35–39].
- Landau–Kleffner syndrome (LKS) is a subtype of ESES [32,33] with temporal, bitemporal or diffuse spikes and waves during NREM sleep associated with acquired epileptic aphasia that may improve when spike waves disappear, but deficits frequently persist [6,40,41].
- West syndrome (WS) is characterized by epileptic spasms and a distinctive EEG pattern, called hypsarrhythmia. The epileptic spasms commonly occur in clusters shortly after awakening, whilst hypsarrhythmia is more evident during early NREM sleep [42,43]; severe hypsarrhythmia has negative prognostic value [44,45], whilst impaired NREM sleep downscaling may impact on the cognitive function of these children [6,46].
- Lennox–Gastaut syndrome (LGS) is a severe epileptic and developmental encephalopathy with multiple seizure types, amongst which tonic seizures that show dramatic activation by NREM sleep are the most characteristic [47].

Awakening epilepsies

Juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic–clonic seizures alone (GTCS-a) are typical representatives, as they are characterized by myoclonic seizures and GTCS respectively that typically occur shortly after awakening from night or daytime sleep. The prevalence of JME is 5%–10% of all epilepsies [48], whilst that of GTCS-a is thought to be lower. In both syndromes, seizures are precipitated by sleep deprivation and forced early awakening, whilst interictal discharges are activated by NREM sleep.

Scenario 1 – suspicion of SRE

The diagnostic pathway to be applied in the case of suspected SRE considers the following steps:

1.1 Clinical history

1.2 Questionnaires and diaries

1.3 Tools for capturing the event at home: home-video recording

1.4 Tools for objective evaluation in the laboratory

For capturing the event: overnight recording [video-EEG/polysomnography (PSG)]

For recording possible associated ictal/interictal abnormalities (daytime standard EEG; daytime

Table 1 Statements on the diagnostic pathway to be applied in the case of suspected sleep-related epilepsy (scenario 1): role of clinical history (1.1); questionnaires and diaries (1.2); tools for capturing the event at home: home-video recording (1.3)

Diagnostic step (evidence base)	Statement

1.1 Role of clinical history (class III studies; expert opinion)	1.1.1 In all subjects with suspected SRE, clinical history should be obtained from the patient and witnesses of the events where at all possible 1.1.2 The history should include the following aspects:
	• *Semiology*
	  • Semiological details including subtle onset symptoms of the event; the description of a dystonic posturing or hyperkinetic movements of a witnessed episode can be suggestive of 'possible SHE'
	  • Stereotypy
	  • Awareness/loss of consciousness.
	  • Position of the patient during events
	  • Features of onset/offset (abrupt or gradual)
	  • Duration
	  • Features after the event (wake or return to sleep?)
	• *Circumstances under which the paroxysmal events occurred*
	  • Triggering, precipitating or facilitating factors
	  • Self-injuries/harm towards self or others
	• *Chronology*
	  • Timing and circadian distribution (day and/or night, sleep/wakefulness? Timing of events during the night)
	  • Frequency of events across the night and over time (weeks, months, years); clusters of events
	  • Evolution of the disorder over time; response to previous treatments
	• *Personal and family medical history, not only of epilepsy but also regarding comorbidities*
	1.1.3 First diagnostic contact(s) may be a neurologist, a child neurologist, an epileptologist, a sleep physician. If the case remains unclear, patient should be referred to specialized centres with expert knowledge in sleep medicine and epilepsy. Follow-up contact may also be done by trained nurses

1.2 Role of questionnaires and diaries (class III and IV studies; expert opinion)	1.2.1 For the majority of SREs there are no validated diagnostic questionnaires 1.2.2 A validated questionnaire, the frontal lobe epilepsy and parasomnias (FLEP) scale, can be used in distinguishing SHE from parasomnias but the limitations of the questionnaire must be recognized 1.2.3 Patient diaries can be helpful in assessing seizure frequency and response to treatment, but the tendency for under-reporting of sleep-related seizures should be recognized
1.3 Role of home-video recording (expert opinion)	1.3.1 In the case of suspicion of SRE home-video recording is not mandatory but it may be helpful in characterizing paroxysmal manifestations for differential diagnosis 1.3.2 In the case of suspicion of SHE, an audio-video documentation through home-video recording, including video captured with smart phones, of at least one hypermotor event may be diagnostic ('video-documented (clinical)' SHE). The event should be confirmed to be typical by witness and should include the onset, the evolution and offset of the attacks 1.3.3 Benefits of home-video recordings are of high sensitivity and might increase specificity, especially when multiple events are recorded

SHE, sleep-related hypermotor epilepsy; SRE, sleep-related epilepsy.

sleep EEG; overnight recording with video-EEG/PSG)

1.1 The role of clinical history for the diagnosis of suspected SRE

Statements, based on class III studies and on expert opinion, are reported in Table 1.

Summary of the evidence

For patients with suspected SRE there is no direct evidence on reliability of clinical history. There is only a single study [49] assessing the accuracy of history elements for the diagnosis of SHE, reporting that the dystonic and hyperkinetic patterns had a high specificity (91.5%) but a low sensitivity. This is a class III study and it has not been independently validated; however, the diagnosis of 'possible SHE' was deemed as sufficient on the basis of history elements [10]. No diagnostic accuracy studies were found for any other SRE.

Clinical history is the basic tool for formulating diagnostic hypotheses and expressing a pre-test probability [50]. 'The diagnosis of epileptic or non-epileptic seizure is almost always based solely on the clinical history. Inadequate history is the most common reason for misdiagnosis' [51]. A systematic review on the management of newly diagnosed patients with

epilepsy concluded that a complete history is the first diagnostic intervention supported by the literature to rule in a diagnosis of epilepsy [52]. These quotes underline the importance of spending ample time taking the history. This should be done in an expert way, often requiring patience and sometimes lengthy questioning. Everyone will agree that an expert should do this, but what is the definition of such a person? The existing literature does not help clarify this [53,54], but experience in the treatment of people with epilepsy is without doubt the major component. The assessment of history taking in patients with SRE or its mimics relies on expert opinions that appear to have high accuracy but are rarely published in scientific journals. For all subjects, the history from both the patient (even young children) and the witnesses is important. Obviously, the report from the witness gets emphasis when the patient is not able to give details, e.g. very young, has learning disability or dementia, or incomplete recollection of events.

The history should be taken by a physician with formal training in epilepsy and should include history from both patient and witnesses. Therefore, history taking by a neurologist or child neurologist is most logical, helped by a sleep physician in cases where these specialists have limited knowledge about sleep medicine. Physician assistants and specialized nurses can often contribute important additions. There is some indirect evidence of effectiveness for specialist nurse practitioners in terms of improving reported knowledge of information and advice received from professionals in patients with any kind of epilepsy [53].

Recommendations for future research

There is a need for large scale studies assessing the diagnostic accuracy of the most discriminating variables of history taking in prospective samples of patients with suspected SRE versus non-epileptic events in sleep.

1.2 The role of questionnaires and diaries for the diagnosis of suspected SRE

Statements, based on class III and IV studies and on expert opinion, are reported in Table 1.

Summary of the evidence

Many questionnaires have been validated for a screening diagnosis of epilepsy without specification of the underlying syndrome (see Keezer *et al*. [55]). A few diagnostic questionnaires could reliably classify GTCS [56–58], but for patients with suspected SRE there is insufficient or no evidence on diagnostic accuracy or on reliability of these questionnaires. The frontal lobe epilepsy and parasomnias (FLEP) scale was designed to distinguish SHE from parasomnias (particularly disorders of arousal), as these conditions can be easily confused. The scale has been validated in two class III studies [59,60] that found high positive and negative predictive values, although a high number of indeterminate intermediate scores were noted and two cases of SHE misclassified as parasomnias highlight its limitations [60]. Moreover, the validation studies have applied the scales to selected patient groups and their reliability in a wider clinical context has not been studied systematically; these scales should be seen as screening tools for clinicians. However, they should not be considered as definitive and do not replace video-EEG/PSG in the diagnostic process.

For patients with suspected SRE there is no evidence on diagnostic accuracy or on reliability of diaries. Patient diaries are useful in individuals with an established diagnosis of epilepsy [61,62]. However, under-reporting of seizures is common [63], especially in SRE [64], particularly if the individual sleeps alone. SHE can be associated with very frequent, but relatively subtle, seizures which may not be recognized by the patient or a bed partner in some cases [65].

Recommendations for future research

There is need of a diagnostic accuracy study of FLEP in a larger scale prospective design.

Formal assessment of patients' accounts / seizure diaries versus objectively recorded seizures during continuous video-EEG monitoring should be carried out to assess under-reporting rates across SRE syndromes.

1.3 The role of home-video recording for the diagnosis of suspected SRE

Statements, based on expert opinion, are reported in Table 1.

Summary of the evidence

For patients with suspected SRE there is no direct evidence on diagnostic accuracy or reliability of home-video recording. Semiology of sleep-related events, as recorded on video, can play a key role in distinguishing sleep-related epileptic seizures from non-epileptic sleep phenomena, predominantly parasomnias [66], and is recommended although no studies on the sensitivity or specificity of this technique exist. The video recording (also home-made) was stated as sufficient for reaching a diagnostic level of 'video-documented (clinical)' SHE [10].

There is some evidence that home-video recording could be feasible and acceptable in recording any type

Table 2 Statements on the diagnostic pathway to be applied in the case of suspected sleep-related epilepsy (scenario 1electroclinical evidence for syndromic classi24): role of tools for objective evaluation in the laboratory for the diagnosis of specific sleep-related epilepsies (1.4)

Diagnostic step (evidence base)	Statement
1.4 Role of tools for objective evaluation in the laboratory	
1.4.1 Sleep-related hypermotor epilepsy (SHE)	1.4.1.1 Sleep EEG detects epileptiform discharges (both interictal and ictal) in about 50% of patients
(class III and IV studies; expert opinion)	1.4.1.2 A video-EEG documentation of the hypermotor event (during sleep) associated with a clear-cut epileptic discharge or with interictal epileptiform abnormalities is definitively diagnostic ('video-EEG-documented – confirmed – SHE'). A 'video-documented diagnosis' ('clinical SHE') may be achieved in the absence of a clear-cut epileptic discharge or interictal epileptiform abnormalities
1.4.2 Self-limited epilepsy with centrotemporal spikes (ECTS)	1.4.2.1 In the case of suspicion of ECTS, awake EEG is diagnostic in the majority of typical cases but a brief spontaneous nap is desirable 1.4.2.2 Daytime sleep EEG appearances are usually diagnostic and can raise awareness about possible unfavourable course (atypical ECTS). Daytime sleep EEG should be considered when: • Awake EEG is inconclusive • Clinical assessment raises the suspicion of evolution to ESES/CSWS • Clinical assessment raises the possibility of structural aetiology and awake EEG shows unilateral CTS
(class III and IV studies; expert opinion)	1.4.2.3 Prolonged video-EEG recording is indicated only for atypical evolution (drop attacks/atypical absences/myoclonic seizures/non-convulsive states)
1.4.3 Panayiotopoulos syndrome (PS)	1.4.3.1 In the case of suspicion of PS, awake EEG is diagnostic in the majority of typical cases; a brief spontaneous nap is desirable 1.4.3.2 Daytime sleep EEG appears almost always diagnostic and should be considered when: • Awake EEG is inconclusive • Clinical assessment raises the suspicion of evolution to ESES • Clinical assessment raises the possibility of structural aetiology and awake EEG shows unilateral occipital spikes or extra-occipital spikes (as in ECTS above)
(class IV studies; expert opinion)	1.4.3.3 Long-term (>24 h) video-EEG recording is generally not helpful due to infrequent seizures
1.4.4 Electrical status epilepticus in sleep (ESES), continuous spike–wave during slow wave sleep (CSWS), including Landau–Kleffner syndrome (LKS)	1.4.4.1 Daytime sleep EEG (including a period of wakefulness for comparison) should be used as the initial diagnostic procedure. If inconclusive, whole-night EEG recording, possibly with polygraphic channels, is recommended. During follow-up, daytime sleep EEG is sufficient to monitor
(class IV studies; expert opinion)	1.4.4.2 A marked increase of spikes during sleep compared to wakefulness must be present. No evidence is available supporting a specific spike–wave index (SWI) threshold for the diagnosis of ESES. A SWI over 50% during NREM sleep from at least 1 h recording of slow wave sleep, but preferably from whole-night recordings, is proposed for the diagnosis of ESES, combined with documented cognitive/behavioural deterioration
1.4.5 West syndrome (WS)	1.4.5.1 In the case of suspicion of WS awake standard EEG may be sufficient to confirm the diagnosis
(class III and IV studies; expert opinion)	1.4.5.2 Sleep EEG, achievable after feeding, is recommended for its higher chances to record hypsarrhythmia, with further recording up to half an hour after awakening, as this increases the possibility to record epileptic spasms 1.4.5.3 EMG polygraphy (from both deltoids) is mandatory to record muscle activation and distinguish between tonic seizures and myoclonus
1.4.6 Lennox–Gastaut syndrome (LGS)	1.4.6.1 Standard awake EEG may detect slow spike–wave discharges pointing to LGS although they are not sufficient for a definitive diagnosis
(class IV studies; expert opinion)	1.4.6.2 Sleep EEG or sleep overnight recordings to capture the fast rhythmic pattern (including EMG from deltoid muscles to detect possibly associated tonic contractions) during NREM sleep is mandatory to confirm diagnosis 1.4.6.3 This EEG pattern may not be present at the onset; therefore repeating of the test during the disease course may be necessary to confirm the diagnosis

(continued)

Table 2 *(Continued)*

Diagnostic step (evidence base)	Statement
1.4.7 Juvenile myoclonic epilepsy (JME) (class IV studies; expert opinion)	1.4.7.1 Awake standard EEG can be diagnostic in 54%–76% of patients with presentation of EEG patterns suggestive of JME. When possible, EEG should be recorded early morning 1.4.7.2 A daytime sleep EEG, especially after sleep deprivation, can be diagnostic in up to 90%. Continuing the recording up to half an hour after awakening increases the likelihood of recording myoclonic jerks. Recommended when awake EEG is not diagnostic 1.4.7.3 EMG polygraphy (from deltoids) is recommended for both awake and daytime sleep EEG 1.4.7.4 Long-term (>24 h) video-EEG recording may improve sensitivity
1.4.8 Epilepsy with generalized tonic–clonic seizures alone (GTCS-a) (class IV studies; expert opinion)	1.4.8.1 Awake standard EEG can be diagnostic in more than half of patients with presentation suggestive of GTCS-a 1.4.8.2 When awake EEG is not diagnostic, a daytime sleep EEG (especially after sleep deprivation) including recording up to half an hour after awakening is recommended 1.4.8.3 Long-term (>24 h) video-EEG recording may improve sensitivity

CTS, centrotemporal spikes; EEG, electroencephalography; EMG, electromyography; NREM, non-rapid-eye-movement.

of seizure [67–70] and reliable in differentiating seizures from other events [71]. Home-video recordings were encouraged to capture events for the diagnosis of infantile seizure [72]. Home-video recordings may be of particular help in distinguishing SHE from parasomnias [73]. Indeed, Derry *et al*. [66] developed a simple algorithm of the semiological features able to correctly identify the vast majority of nocturnal episodes.

Electronic equipment to video the events is widely available. Smart phones and infrared, motion-activated cameras are cheap and provide acceptable quality. Instructions to bed partners or family members about how to obtain video recordings with optimal details should be given (including the whole body in view, patients sufficiently dressed in order to avoid bedclothes covering the body to enable better semiological analysis). When the paroxysmal events are relatively rare, home monitoring spares the patients the inconvenience of very long monitoring-unit stays and improves the sensitivity by capturing many more events [74–76]. Motion-activated systems and video recordings triggered by accelerometers may reduce the total video length to be reviewed by the physician [77]. Videos of typical nocturnal events which are often available in the epilepsy clinic may be shown to the patient and, in particular, to witnesses to provide examples of semiologies to compare with the patient's events. An informed consent should be obtained from the person of whom the video was recorded before showing it to others.

Recommendations for future research

The actual sensitivity and specificity of home-video recording are unknown. Future studies should evaluate these aspects. The following questions should be addressed:

- The diagnostic accuracy of home-video recording for the differential diagnosis of SRE versus parasomnias;
- The burden of the additional monitoring on patients;
- Improved technical solutions for event-capturing using home video.

1.4 The role of tools for objective evaluation in the laboratory for the diagnosis of suspected SRE

Sleep-related hypermotor epilepsy (SHE). Statements, based on class III and IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. Around 50% of sleep EEG (compared to 12%–33% of wake EEG) show interictal epileptiform discharges [10,65,78,79]. Video-EEG documentation of the events during sleep, with at least 19 EEG channels (10–20 international system), electrocardiogram, oculogram and chin electromyography (EMG) is recommended [10,65,66]. However, interictal and ictal scalp EEG features may be uninformative because of EEG artefacts or when seizures originate from the deep-seated cortex [65,80]. PSG may aid in the differential diagnosis (versus sleep disorders) in selected cases [10,81,82].

1.4.2 Self-limited epilepsy with centrotemporal spikes (ECTS). Statements, based on class III and IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. In a cohort of children with a first unprovoked seizure, EEG epileptiform abnormalities suggestive of ECTS were present in about 10% of cases [83]. Standard EEG sensitivity ranges from 63% to 92% [84–90] with a specificity of 60% [84] and false positive 28% (no epilepsy) [91]. Sensitivity of sleep EEG (N1–N2 are sufficient for activation

of centrotemporal spikes) is reported to be 100% in most studies [84,85,87,88]; specificity data are not available. In subjects with centrotemporal spikes the presence of ripples on Rolandic spikes has been shown to be a predictor of seizure occurrence (area under the curve 0.84; 95% confidence interval 0.63–0.99) [92]. Some interictal sleep EEG patterns and their long-lasting persistence (6 months) seem to be the hallmarks for neuropsychological impairments [93]. Structural aetiology could be suspected when awake EEG shows unilateral centrotemporal spikes [94–96]. When atypical evolution is clinically suspected (drop attacks/atypical absences/myoclonic seizures/non-convulsive states) prolonged video-EEG recording is indicated [97].

1.4.3 Panayiotopoulos syndrome (PS). Statements, based on class IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. Sensitivity of standard EEG for occipital spikes and extra-occipital spikes is reported to be around 66% [98,99] with only one study [100] reporting higher levels (92.3%). Sensitivity of sleep EEG (N1–N2 are sufficient for activation of spikes) is higher (78%–100%) [98,99,101,102]. Specificity data are not available. As seizures are infrequent, prolonged video-EEG recording is not considered useful [97].

1.4.4 Electrical status epilepticus in sleep (ESES), continuous spike–wave during slow wave sleep (CSWS), including Landau–Kleffner syndrome (LKS). Statements, based on class IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. Diagnostic criteria for ESES/CSWS (including LKS) are heterogeneous and no consensus exists in the literature. Awake standard EEG recording is not indicated. Daytime sleep EEG, including wake pre-sleep, is an appropriate initial procedure to demonstrate the enhancement of epileptic activity during NREM sleep [32,97,103–106]. If inconclusive, overnight EEG/polygraphic recording is indicated [30,97,106]. A few data suggest that ambulatory EEG might be an alternative procedure [107]. Epileptic activity can occur in a (sub)-continuous, periodic or fragmented fashion and the topography can be diffuse, unilateral, focal or multifocal [30,32].

Evidence has been reported showing the occurrence of a cognitive/behavioural deterioration associated with a wide range of spike–wave indices (from 25% to 100%) [106,108,109]. Therefore, the concept of a minimum spike–wave index (SWI) necessary for the diagnosis of ESES should be flexible (although an SWI ≥50% has been used in the vast majority of studies), once the main feature of ESES, i.e. occurrence of cognitive deterioration associated with sleep-enhanced epileptic activity, is demonstrated [110].

The SWI can be calculated using visual evaluation or semi-automated quantitative methods, based on spike-detection algorithms [111–116]. The SWI should be calculated from a recording with NREM sleep of at least 1 h or long enough to include a complete NREM–REM sleep cycle, but preferably from whole-night recordings [111].

Once the diagnosis has been confirmed, daytime sleep EEG may be sufficient to monitor EEG evolution and response to treatment in the follow-up [97].

1.4.5 West syndrome (WS). Statements, based on class III and IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. The standard EEG in wakefulness may show the typical hypsarrhythmia pattern [117]. Hypsarrhythmia predicts seizure recurrence (83% vs. 17% in normal EEG) [118]. Sleep EEG is preferred, as hypsarrhythmia is more common during sleep [97,117,119,120]. Four-hour recordings appear to be sufficient to record spasms in nearly all patients, provided that waking, sleep and awakening are included in the recording [121]. Video-EEG, including EMG polygraphic channels, is particularly useful in recognizing subtle spasms [121].

1.4.6 Lennox–Gastaut syndrome (LGS). Statements, based on class IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. A standard EEG recording can demonstrate bilateral synchronous slow spike–wave discharges, with or without overt clinical correlate [47,122]. However, this pattern is not specific to LGS [122]. Daytime sleep EEG can show bursts of diffuse or bilateral fast rhythm patterns (run of rapid spikes) during NREM sleep in 37%–100% of cases [47,122,123]. Clinical correlates may be subtle (brief apnoea, mild axial contraction) or overt (i.e. tonic seizure). Polygraphic assessment with surface EMG recording (usually from both deltoids) to detect tonic seizures is recommended [97]. Overnight sleep video-EEG/PSG may be performed in selected cases when daytime sleep EEG is not conclusive.

1.4.7 Juvenile myoclonic epilepsy (JME). Statements, based on class IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. The sensitivity of standard EEG ranges between 54% and 76% [124–130]. Intermittent photic stimulation to detect EEG photosensitivity is recommended. The sensitivity of sleep EEG ranges between 76% and 89.5% [130–132]. N2 stage is mandatory as this provides a higher yield. EEG after sleep deprivation increases diagnostic sensitivity in patients with idiopathic generalized epilepsy [133].

In some patients, long-term video-EEG recordings may be necessary to achieve sufficient electroclinical evidence for syndromic classification [134,135].

1.4.8 Epilepsy with generalized tonic–clonic seizures alone (GTCS-a). Statements, based on class IV studies and on expert opinion, are reported in Table 2.

Summary of the evidence. The sensitivity of standard EEG ranges between 53% and 87.5% [126,136,137]. The sensitivity of sleep EEG ranges between 62% [136] and 92% [138]. EEG after sleep deprivation increases diagnostic sensitivity in patients with idiopathic generalized epilepsy [133,139]. Stages N1–N2 are sufficient for activation of generalized spike–wave discharges [137]. Recording upon awakening may increase the diagnostic specificity for GTCS-a (by detecting previously unsuspected absences that are an exclusion criterion and indicate another syndrome) and can reveal generalized spike–wave discharges [140]. In some patients, prolonged EEG or long-term video-EEG recordings may be necessary to achieve sufficient electroclinical evidence for syndromic classification [134].

The diagnostic pathways in case of suspicion of SRE are reported in Fig. 1 (general scheme) and Fig. 2 (syndrome specific schemes).

1.5 Recommendations for future research

Diagnostic studies on SRE are limited by the scarcity of well designed studies. The commonest flaws regard the exclusion of patients at the suspicion stage of disease (hindering the computation of specificity), the absence of any long-term follow-up (useful element to confirm the diagnosis when lacking a true reference standard) and low power samples. These issues are justified by the relative rarity of these conditions and the uncertain diagnostic boundaries of some of them. International collaborations using common sets of clinical data and the use of standardized methods when a diagnostic study is designed [141] could overcome these limits.

Although other genetic (idiopathic) generalized epilepsy syndromes are not formally included in the SRE, these may have a similar relationship with sleep to that of JME and GTCS-a. Further full EEG montage PSG or home-video telemetry studies employing EMG and respiratory polygraphy are needed to explore electrographic behaviours of generalized spike–wave discharges, including their occurrence in sleep-stage/sleep-wake transitions and their possible effects on sleep macrostructure and microstructure.

Currently, the incidence and prevalence of SHE is probably underestimated, due to its varied clinical presentation which also includes minor seizures and the difficulties in its differentiation mainly from arousal disorders. Further full EEG montage PSG or home-video telemetry studies employing EMG and respiratory polygraphy are needed for:

- Fuller characterization of hyperkinetic and dystonic seizures and better understanding of the frequency of minimal motor events and simple arousals that may pass unnoticed;
- Validation of the diagnostic criteria to differentiate SHE seizures from arousal disorders as proposed by Derry *et al*. [66] and Proserpio *et al*. [82] and establishing their specificity and sensitivity;
- Enabling multicentre studies of the familial co-occurrence of SHE with arousal disorders to elucidate potential shared genetic susceptibility [10, 142].

In paediatric SRE, further clinical research using all-night full EEG montage PSG or home-video-EEG telemetry with respiratory and EMG polygraphy are needed:

- In children diagnosed with self-limited ECTS and PS, who show atypical evolution [25], including language and cognitive dysfunction and possible sleep-related enhancement of epileptic discharges;
- In children with LGS to understand the effect of interictal epileptic discharges and mild tonic seizures on sleep;
- At multicentre international level together with neuropsychological evaluation to agree on widely accepted diagnostic criteria for ESES.

Scenario 2 – SRE and comorbidity with sleep disorders

Comorbid sleep disorders and subsequent sleep deprivation may interfere with seizure control [19]. The same general current International Classification of Sleep Disorders (ICSD) criteria for SDB, insomnia and RLS diagnoses apply in patients with controlled SRE. The diagnostic and management pathway to be applied in the case of SRE and suspected comorbid sleep disorders (SDB, insomnia, RLS) include the following steps:

2.1 Clinical history
2.2 Questionnaires and diaries
2.3 Further diagnostic workup (tests)
2.4 Management/treatment

2.1 The role of clinical history for the diagnosis of suspected comorbid sleep disorders (SDB, insomnia, RLS) in patients with SRE

Statements, based on clinical practice guidelines and on expert opinion, are reported in Table 3.

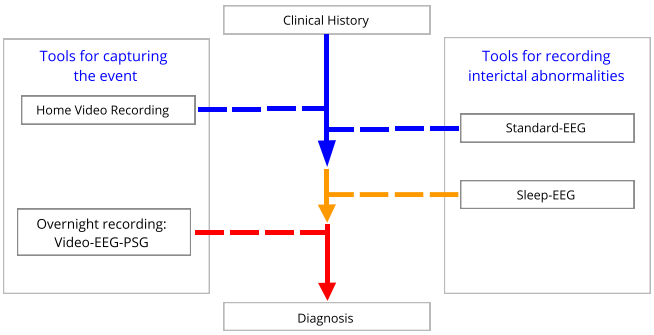

Figure 1 General diagnostic pathway scheme for objective evaluation in the laboratory in the case of suspicion of SRE. Lines: in blue diagnostic tools in primary services, in yellow diagnostic tools in secondary services, in red diagnostic tools in tertiary services; continuous line, mandatory test; dotted line, tool suggested in particular cases.

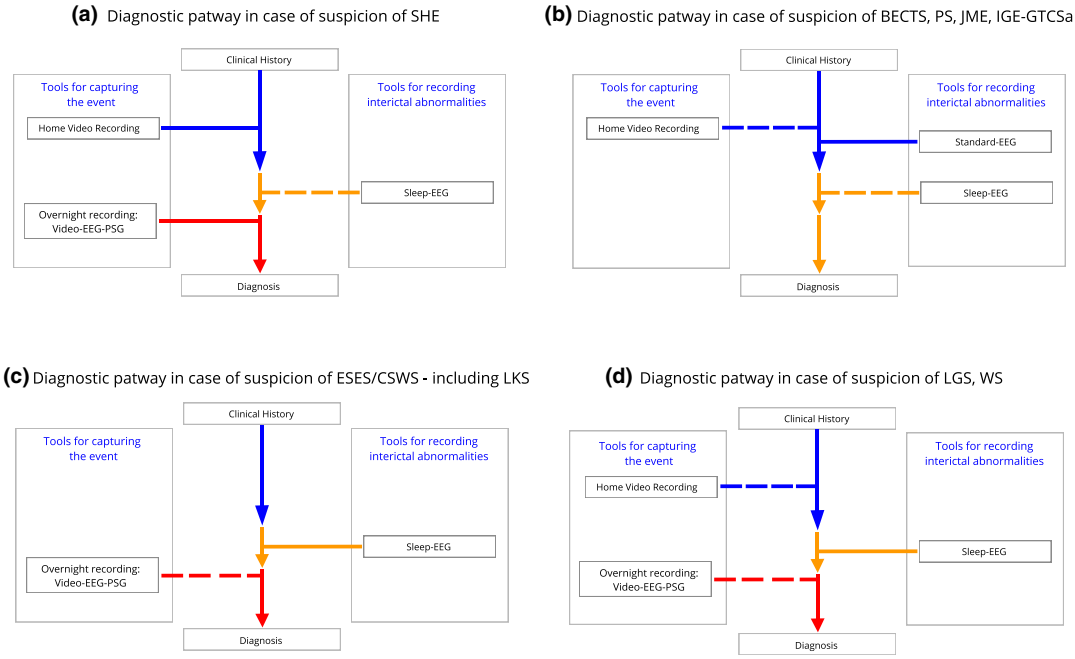

Figure 2 Diagnostic pathway scheme for objective evaluation in the laboratory in the case of suspicion of (a) sleep-related hypermotor epilepsy (SHE); (b) self-limited epilepsy with centrotemporal spikes (BECTS), Panayiotopoulos syndrome (PS), juvenile myoclonic epilepsy (JME), epilepsy with generalized tonic–clonic seizures alone (IGE-GTCSaw); (c) electrical status epilepticus in sleep, continuous spike–wave during slow wave sleep, including Landau–Kleffner syndrome (ESES/CSWS, including LKS); (d) Lennox–Gastaut syndrome (LGS), West syndrome (WS). Lines: in blue diagnostic tools in primary services, in yellow diagnostic tools in secondary services, in red diagnostic tools in tertiary services; continuous line, mandatory test; dotted line, tool suggested in particular cases.

Summary of the evidence

There are no studies on the diagnostic accuracy of clinical history for suspected comorbid sleep disorders in patients with SRE. Clinical practice guidelines report the elements of clinical history to be used when comorbid sleep disorders are suspected: SDB in children [143]; SDB in adults [144]; insomnia in adults [145]; RLS in children [146]; RLS in adults [147].

Symptoms typically associated with comorbid sleep disorders, such as daytime sleepiness, fatigue and non-restorative sleep, may be caused by antiepileptic drug treatment as well as seizure occurrence in epilepsy patients. This may reduce the diagnostic accuracy of the clinical history. However, symptoms such as non-restorative sleep and daytime sleepiness should always be assessed and history of witnessed snoring, observed apnoeas, overweight patients and facial dysmorphisms

should raise the clinical suspicion of comorbid SDB and trigger further investigations.

2.2 The role of questionnaires and diaries for the diagnosis of suspected comorbid sleep disorders (SDB, insomnia, RLS/periodic limb movement disorder) in patients with SRE

Statements, based on clinical practice guidelines and on expert opinion, are reported in Table 3.

Summary of the evidence

Many questionnaires have been developed to improve the diagnostic accuracy of SDB, insomnia and RLS. The vast majority are not validated for patients with epilepsy (none for SRE). Amongst others (Berlin Questionnaire, Epworth Sleepiness Scale, Multivariate Apnoea Prediction Index, Pittsburgh Sleep Quality Index, STOP-BANG Questionnaire, STOP Questionnaire, Multivariable Apnoea Prediction Questionnaire), the STOP-BANG Questionnaire seems to be more accurate for detecting SDB [148–150]. Clinical practice guidelines do not recommend the use of questionnaires as screening tools for SDB because of the less than desirable diagnostic accuracy with subsequent high risk of false negative and false positive results [151,152]. The Sleep Apnoea Scale of the Sleep Disorders Questionnaire (SA-SDQ) is the only questionnaire which has been validated for the screening of SDB in epilepsy populations. Weatherwax *et al*. [153] indicated screening cut-offs of 29 for men and 26 for women. More recently Economou *et al*. [154] indicated a single cut-off score (of 25) for predicting obstructive sleep apnoea in adults with epilepsy. An observational study suggests that the STOP-BANG Questionnaire might improve the detection of epilepsy patients at risk for obstructive sleep apnoea [155].

Clinical practice guidelines recommend the use of questionnaires and sleep diaries for insomnia at baseline and treatment outcome assessment [145,156]. The Insomnia Severity Index, Pittsburgh Sleep Quality Index and Dysfunctional Beliefs and Attitudes about Sleep Questionnaire are suggested as possible diagnostic tools [156]. A recent systematic review [16] on insomnia in people with any kind of epilepsy found 31 studies. In adult patients with epilepsy, insomnia prevalence was around 28.9%–51% based on the Insomnia Severity Index and 36%–74.4% based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR), or the ICSD-2. The prevalence of insomnia in children with epilepsy was around 13.1%–31.5% using the Sleep Disturbance Scale for Children and 11% based on ICSD-2 diagnostic criteria. Insomnia was related to poor seizure control in some studies but not all [16]. Poor sleep quality, assessed by the Pittsburgh Sleep Quality Index, was more prevalent in JME patients than in controls [157–160].

The diagnosis of RLS is based on the recognized international criteria for children [146] and adults [147]. The application of diagnostic criteria was used to assess the prevalence of RLS in patients with temporal epilepsy [13] or unspecified epilepsy [161]. In a recent systematic review [162] the Cambridge–Hopkins diagnostic questionnaire for RLS (CH-RLSq) and the Restless Legs Syndrome – Diagnostic Index (RLS-DI) were recommended for clinical practice purposes in order to improve diagnostic accuracy; no tool is available for children.

Questionnaires for evaluating daytime sleepiness may be helpful for detecting symptoms possibly related to an undiagnosed sleep disorder [163].

2.3 The role of tests for the diagnosis of suspected comorbid sleep disorders (SDB, insomnia, RLS) in patients with SRE

Statements, based on clinical practice guidelines and on expert opinion, are reported in Table 3.

Summary of the evidence

Clinical practice guidelines define the general indications for actigraphy, home sleep testing and PSG when any of the considered sleep disorders is suspected: SDB in children [143,164], SDB in adults [151,152], insomnia in children [165], insomnia in adults [145,156,165], RLS in children [81] and RLS in adults [166]. The same indications could be used in patients with stable SRE.

In patients with non-stable forms of SRE, in laboratory or ambulatory video-PSG with extended EEG montages are considered appropriate to diagnose SDB and other comorbid sleep disorders as well as unreported nocturnal epileptic seizures contributing to sleep disruption.

2.4 Treatment for SDB, insomnia, RLS effective in patients with SRE

Statements, based on class II and III studies, clinical practice guidelines and on expert opinion, are reported in Table 3.

Summary of the evidence

Continuous positive airway pressure (CPAP) treatment is effective (odds ratio 5.26, 95% confidence interval 2.04–13.5) in reducing seizure occurrence (50% reduction in seizure rate or seizure-free rate)

Table 3 Statements on the diagnostic and management pathway to be applied in the case of SRE and suspected comorbid sleep disorders (SDB, insomnia, RLS) (scenario 2): role of clinical history (2.1); questionnaires and diaries (2.2); further diagnostic workup (2.3); management/treatment (2.4)

Diagnostic step (evidence base)	Statement
2.1 Role of clinical history (clinical practice guidelines; expert opinion)	2.1.1 Clinical history for assessing comorbid sleep disorders should be obtained from patients and bed partners in all subjects with SRE (even if the patient is not complaining of any sleep-related problems) 2.1.2 Most symptoms and signs suggestive of comorbid sleep disorders by ICSD current criteria can be assessed by history 2.1.3 Daytime sleepiness should be assessed in specific situations such as in patients with a driving licence 2.1.4 Clinical history for assessing comorbid sleep disorders should start with open questions on general aspects of disturbed or non-restorative sleep and daytime sleepiness with more focused questions in the case of positive findings 2.1.5 The first diagnostic contact should be with a neurologist, child neurologist, epileptologist, or a sleep physician with interest in epilepsy. The management of the most complex cases should be transferred to specialized centres. 2.1.6 Follow-up contact: may also be done by trained nurses and physician assistants
2.2 Role of questionnaires and diaries (clinical practice guidelines; expert opinion)	2.2.1 In the case of suspicion of comorbid sleep disorders, questionnaires and diaries could facilitate recording of clinical features in a standardized way although these are not specifically validated for patients with SRE
2.3 Role of tests (clinical practice guidelines; expert opinion)	2.3.1 The usual indications for actigraphy, home sleep testing and PSG for the diagnosis of SDB, insomnia, RLS apply to patients with controlled SRE 2.3.2 All uncontrolled SRE patients with a clinical suspicion of a sleep disorder should be further investigated with home sleep studies or inpatient video-PSG (full 10–20 electrode set)
2.4 Treatment for sleep-disordered breathing, insomnia, restless leg syndrome effective in patients with SRE (class II and III studies; clinical practice guidelines; expert opinion)	2.4.1 Any condition leading to sleep disruption and sleep deprivation should be recognized and treated according to standard procedures. Considering the high frequency of the disorders the following situations are highlighted: 2.4.2 Sleep-disordered breathing (class II, III; expert opinion) • To treat comorbid SDB in SRE is likely to be beneficial for seizure control • Treating SDB should be considered independently of its severity in non-seizure-free patients. Benefit of SDB treatment on seizure reduction and sleepiness must be controlled by follow-up • AEDs (causing sedation, muscle relaxation and/or weight gain) and VNS may worsen (or induce) SDB 2.4.3 Insomnia (clinical practice guidelines; expert opinion) • Cognitive behavioural therapy (CBT) and chronobiologically based therapy are considered as first line choice for treatment of insomnia in subjects with SRE • Caution should be adopted in using sleep restriction procedure as it may induce sleep deprivation that may provoke seizures in patients with epilepsy • Short-term treatment of chronic insomnia may include pharmacological treatment avoiding drugs lowering seizure threshold 2.4.4 Restless leg syndrome (clinical practice guidelines; expert opinion) • Restless leg syndrome should be treated if it is associated with sleep deprivation or fragmentation according to current standard recommendations

AEDs, antiepileptic drugs; ICSD, International Classification of Sleep Disorders; PSG, polysomnography; RLS, restless leg syndrome; SDB, sleep-disordered breathing; SRE, sleep-related epilepsy; VNS, vagus nerve stimulation.

versus no CPAP in patients with any kind of epilepsy (refractory or not), according to a meta-analysis [167] (one class II quality [168]; two class III quality [169,170]). Treating SDB should be considered independently of its severity in non-seizure-free patients [163]. Since patients with epilepsy seem to be less adherent to CPAP therapy, they might need careful monitoring of treatment [171]. The benefit of SDB treatment on seizure reduction and sleepiness must be evaluated at follow-up. Vagus nerve stimulation may worsen or induce SDB [172].

Treatment of chronic insomnia and RLS/periodic limb movement syndrome is beneficial in SRE based on the general assumption that increased sleep

fragmentation and shortened sleep duration can have deleterious effects on seizure frequency and daytime sleepiness.

Cognitive behavioural therapy is considered first line choice of treatment of chronic insomnia [145] and appears suitable to treat insomnia comorbid with epilepsy [173]. However, caution should be adopted in using sleep restriction as part of cognitive behavioural therapy because it may cause sleep deprivation which can be detrimental to seizure control in epilepsy patients [16].

Pharmacological treatment may be used in treating insomnia in epilepsy patients provided that short-term treatment is used with drugs that do not interfere with seizure threshold [174].

There are no specific studies of the treatment of RLS in patients with epilepsy. According to a panel consensus, RLS should be treated according to clinical practice guidelines [81,175,176].

2.5 Recommendations for future research

Further studies should be conducted in order to validate sleep disorder questionnaires for patients with SRE.

Further studies are needed to evaluate the impact of the treatment of comorbid sleep disorders such as insomnia and RLS on seizure outcome in patients with SRE.

Conclusions

Sleep-related epilepsies represent a significant proportion of all epilepsies. However, definitive criteria for evaluating patients with SRE are lacking. The recommendations provided by this consensus review could be of help for standardizing and improving the diagnostic approach and accuracy of specific SRE.

The importance of identifying and treating specific sleep disorders to improve the management and outcome of patients with SRE is stressed.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Methods, search strategies, literature search results.

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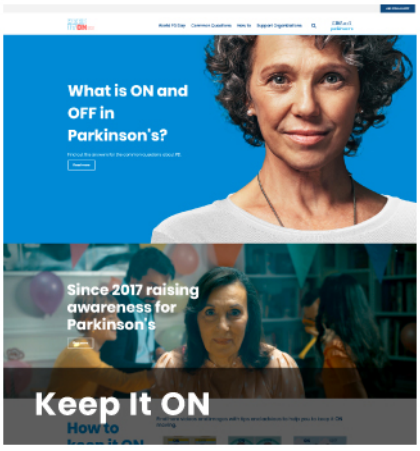

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