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Summary

New diagnostic criteria define epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. Two factors are associated with an increased risk of relapse: the presence of a cerebral lesion and epileptiform abnormalities (EA) in the electroencephalogram (EEG). In this paper we focus on the risk of relapse after a first unprovoked seizure; we review the yield of standard and sleep EEG to identify EA and/or abnormal but unspecific slowing. Sensitivity is defined as the percentage of EEG with EA, when epilepsy is present; specificity as the percentage of presence of epilepsy, when EEG shows EA. Main findings are: 1) Sensitivity and specificity of interictal EA are: 17% and 95% for adults, and 58% and 70% for children. An adult presenting with a first unprovoked seizure has a 77% post-test probability of relapse if routine EEG includes EA and 47% if it does not (focal and generalized discharges confounded). Percentages for children are slightly lower than adults (66% and 38%). 2) There is an increased yield if routine EEG is performed within 24 hours after seizure (51% in a mixed population of children and adults). 3) Identification of EA after the third normal standard wake EEG is extremely low. Sleep EEG increases significantly the likelihood to detect EA, i.e. with up to 50%. Standard EEG carries valuable information with respect to the underlying syndrome and risk of relapse. If negative, we propose to obtain a sleep recording, including the first 2 hours after awakening.

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Key words: First seizure, relapse risk, drug treatment, MRI

EEG nach erstem unprovoziertem Anfall – welche Zusatzinformation können wir erwarten?

Die neuen diagnostischen Kriterien für Epilepsie definieren diese Erkrankung als eine andauernde Prädisposition, Anfälle zu generieren. Zwei Faktoren sind mit einem Rückfallrisiko assoziiert: das Vorhandensein einer zerebralen Läsion und epileptogene Anomalien (EA) im Elektroenzephalogramm (EEG). In diesem Artikel diskutieren wir das Risiko eines Rückfalls nach einem ersten nicht-provozierten Anfall und den Ertrag von Standard- und Schlaf-EEG zur Identifizierung von EA und/oder unspezifischen EEG-Verlangsamungen. Sensitivität ist definiert als die Fähigkeit des EEGs, EA zu entdecken, wenn eine Epilepsie vorhanden ist; Spezifizität bezieht sich auf die Wahrscheinlichkeit, Epilepsie zu diagnostizieren, wenn das EEG EA zeigt. Hauptergebnisse: 1) Sensitivität und Spezifizität von EA sind 17 % und 95 % für Erwachsene sowie 58 % und 70 % für Kinder. Ein Erwachsener hat eine Rückfallwahrscheinlichkeit von 77 %, wenn das EEG EA zeigt, und 47 %, wenn das nicht der Fall ist. Die Zahlen für Kinder sind etwas niedriger (66 % und 38 %). 2) Der Gewinn eines Standard-EEGs ist höher, wenn es innerhalb von 24 h nach dem Anfall durchgeführt wird (51 % in einer gemischten Patientenpopulation von Kindern und Erwachsenen). 3) Die Wahrscheinlichkeit, doch noch EA zu finden, wenn das 3. Standard-EEG normal ist, ist extrem niedrig. Die Ausbeute kann deutlich erhöht werden durch ein Schlaf-EEG, d.h. bei 23 - 50 % mehr Patienten kann eine Epilepsie diagnostiziert werden. Das Standard-EEG enthält wertvolle Informationen bezüglich des zugrundeliegenden Syndroms und Rückfallrisikos. Falls negativ, empfehlen wir, ein Schlaf-EEG durchzuführen, welches alle Schlafstadien sowie die ersten 2 Stunden nach dem Erwachen umfasst.

Schlüsselwörter: Erstanfall, Rückfallrisiko, medikamentöse Behandlung, MRT

Contribution de l'EEG au diagnostic épileptique après une première crise non provoquée

L'épilepsie est une affection cérébrale caractérisée par une prédisposition durable à générer des crises d'épilepsie. Deux facteurs sont associés à une augmentation des récidives : la présence d'une lésion cérébrale et une anomalie épileptiforme (AE) à l'électroencéphalogramme (EEG). Dans ce papier, nous mettons l'accent sur le risque de récidive après une crise non provoquée et revoyons la place de l'EEG standard et de l'EEG de sommeil dans l'identification des AE et/

ou autres anomalies non spécifiques. La sensibilité est définie comme la capacité de l'EEG à détecter les AE lorsque la maladie est présente; la spécificité est définie comme le risque d'avoir la maladie lorsque l'EEG révèle une AE. Voici nos conclusions principales: 1) la sensibilité et la spécificité d'une AE interictale sont : 17% et 95% pour les adultes, 58% et 70% pour les enfants. Un adulte se présentant avec une première crise non-provoquée a une probabilité post-test de récidive de 77% lorsque l'EEG montre une AE et de 47% en l'absence d'AE (décharges focales et généralisées confondues). Le pourcentage chez les enfants est discrètement plus bas (66% et 38%). 2) L'EEG de routine est de meilleur rendement lorsqu'il est réalisé dans les 24 heures après la crise (51% d'anomalies dans une population mixte d'adultes et d'enfants). 3) L'identification d'une AE après le troisième EEG est extrêmement faible. L'EEG de sommeil augmente significativement la probabilité de détecter une AE et ceci jusqu'à 50%. L'EEG standard nous informe surtout sur la présence d'un syndrome épileptique et du risque de récidive. Si ce dernier est négatif, un EEG de sommeil, incluant les premières heures après l'éveil, est de mise.

Mots clés : Première crise, risque de récidive, traitement médicamenteux, IRM

1. First seizure and epilepsy: current definition and epidemiology

Epilepsy is one of the most frequent neurological diseases, affecting between 0.5 - 1% of the population, i.e, approximately 50 Mio people worldwide [1]. In 2005, a task force directed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy defined epilepsy as "A disorder characterized by an enduring predisposition of the brain to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition" [2]. A commonly used operational definition employed for epidemiological purposes considers a diagnosis of epilepsy after 2 unprovoked seizures occurring at least 24 hours apart [3]. Studies showed that after 2 unprovoked non-febrile seizures, the probability of having another seizure was 73% [3] at 5 years (95% CI is 59 - 87%) versus 40 - 52% after a single unprovoked seizure [1].

Nowadays, the "two unprovoked seizures" definition appears to be inadequate in several clinical circumstances. In 2009, Hesdorffer showed that a patient who presented with a single unprovoked seizure after a remote brain insult, such as stroke, tumor, central nervous system infection or trauma is at high risk of a second unprovoked seizure. This risk is comparable to the risk for further seizures after 2 unprovoked seizures [4]. The same is true for distinct epileptic syndromes (like juvenile myoclonic epilepsy), reflex epilepsy or a single symptomatic seizure of a focal cortical dysplasia [5].

Regarding these considerations, in 2014, the task force of the ILAE re-considered the diagnosis of epilepsy by any of the following conditions [6]:

- At least two unprovoked seizures occurring more than 24 hours apart
- One unprovoked seizure and a probability for further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%)
- At least two seizures in a setting of reflex epilepsy

The threshold of 60% is considered as estimation and not as strict cut-off. This number is based on the risk of relapse after two unprovoked seizures, which is about 60% at 2 years and 70 - 75% at 5 years of follow-up. It requests a workup to calculate the individual risk of predisposition for further seizures.

As we will discuss below ("Risk of relapse"), two factors are consistently associated with an increased risk of relapse: the presence of cerebral lesion and epileptiform abnormalities in the EEG. Seizures clustering within 24 hours confer approximately the same risk for later seizure as a single seizure [7]. Thus, two or more seizures occurring in a 24-hour period are considered to be a single unprovoked seizure.

High risk for recurrence after a single seizure should lead to the consideration of starting an antiepileptic treatment already after the first seizure. In that case, the risk of recurrent seizures, at least during the first 2 years, is significantly reduced by an average of 34% [8]. However, the long-term prognosis is not changed; for this reason, when a lesion is present, the possibility of surgery should be brought up already during the first consultation.

2. Routine EEG in first seizure

Routine EEG should be performed within 24 hours of the first seizure. Indeed a prospective study on 300 consecutive patients showed that interictal epileptiform abnormalities (EA) were present in 51% of patients who underwent an EEG within the first 24 hours, compared to 34% of the patients who had a later EEG [9]. However, it is of note that this study included many children, which differ from adults in terms of occurrence likelihood of discharges. Several studies have shown that interictal EA are more frequent after seizures (postictal activation) [10, 11]. Although these studies were performed on chronic epilepsy, it seems that this increased frequency also applies to new-onset epilepsies [9]. Unfortunately in many cases, scheduling of early EEG is not feasible. On the other hand, very early EEG may show transient, less specific abnormalities, like postictal slowing, which must be interpreted cau-

tiously, as they can also result from the presence of a lesion and are not necessarily a sign of epileptogenicity [12]. An exception are rhythmic delta, extratemporal or temporal, which usually indicates the presence of seizures [13].

Routine EEG should be performed with at least 21 electrodes, placed according to the standard 10 - 20 system and last at least 20 minutes. It is recommended that hyperventilation of 3 minutes and intermittent photic-stimulation at 1 - 50 Hz with the eyes open and closed at each frequency are carried out. The placement of additional inferior temporal electrodes (F9, T9, P9 and F10, T10, P10) is of extreme importance in particular if temporal seizures are searched, a frequent constellation in adults.

Accurate classification of seizure type will help clinicians in diagnostic and therapeutic decisions. Clinical history is fundamental, but unfortunately, after a first episode, this is fraught with limitations due to the lack of witnesses, or peri-ictal amnesia. King et colleagues [9], on a population of 300 patients (20% below 16 years, range 5 - 83 years), were able to classify seizures into focal versus generalized in just 47% of cases after considering medical history and physical examination findings alone. When EEG findings were also taken into account, correct classification was possible in an additional 30%; thus, in their study group, only 23% of seizures remained unclassified. Specific syndromes also influence the likelihood of seeing EA on EEG, with higher rates in patients with absence seizures (92%) and atonic or myoclonic seizures (85%) compared with focal seizures (59%) [14].

What is the relevance of non-epileptiform abnormalities, such as focal slow activity, regional attenuation, or abnormalities of background cerebral rhythms? They are much less specific risk predictors than EA, although they can imply localized structural pathology underlying the seizure disorder, or diffuse cortical dysfunction as in symptomatic generalized epilepsies [15]. Non-epileptiform abnormalities are more common in symptomatic cases (25%) than in idiopathic epilepsy syndromes (7%) [14, 16]. As stated above, rhythmic focal delta usually indicate active epileptogenicity.

What happens if the first routine EEG is normal? A retrospective study on 619 patients reveals that the cumulative yield of EA is 39% after the first EEG study and 68% after the third. Beyond the 3rd EEG, the probability to find epileptiform abnormalities is very low. Thus, at this point a sleep EEG should be requested if this was not yet done before [17].

3. Sleep EEG

The yield of EEG can be significantly increased in all age groups by the use of sleep recording. Indeed sleep states influence the presence of interictal and ictal epileptic activity. Particularly, non-rapid eye movement (NREM) sleep has been characterized as a state of relative "neuronal synchronization". Such coordinated synaptic activity allows the recruitment of a critical mass of neurons, necessary to initiate and sustain epileptic activity [18]. This is why interictal (mainly focal) EA are more common in NREM sleep than in awake recordings. Carpay et al. [14] reported that 60 of 177 (34%) children with normal findings during a standard recording showed EA after sleep deprivation (mostly during sleep). Similarly, King et al. [9] reported that 35% of adults and children whose initial EEG findings were normal, showed EA in a subsequent study performed during sleep. Overall, the literature suggests that sleep EEG increases the yield of significant EEG abnormalities by 30 - 35%.

Whereas NREM sleep may "unmask" the EA that are not present on awake state, REM sleep is reported to show fewer EA. However, REM recordings show a more limited electric field of EA, i.e. corresponding to the true irritative region and thus contributing to localization of the epileptogenic focus [19, 20]. Shinnar et al. [16] described 148 children with unprovoked first seizure who had both sleep and wakefulness recorded on a single EEG. EA were identified either only while awake or only while asleep in 30% of subjects, and in both states in 70% of subjects. While generalized discharges are more common during the awake state, focal discharges are more easily detected during the sleep state.

Sleep recording can be also useful to detect epileptic seizures, of which patients can be unaware. NREM sleep activates frontal lobe seizures more than temporal lobe seizures, and temporal lobe seizures are more likely to secondarily generalize during sleep than during wakefulness [21, 22]. A variety of epilepsy syndromes occur predominantly or exclusively during NREM sleep, or during awaking phases. For example, EEG in patients suffering from "grand mal on awakening" may have a completely normal routine EEG, but very active and frequent EA just before awakening (**Figures 1** and **2**). Other striking examples are the syndrome of continuous spike-wave activity during slow-wave sleep, defined by an EEG pattern consisting of generalized slow-spike-wave discharges present for 85 - 90% of slow-wave sleep and relatively suppressed during REM sleep and wakefulness, and the Landau-Kleffner syndrome. These syndromes, characterised by a continuous spike-wave in slow sleep, start in early to mid-childhood and lead to cognitive regression and seizures. Early, appropriate treatment is indicated to attempt to ameliorate the electrical status and improve the child's cognitive function.

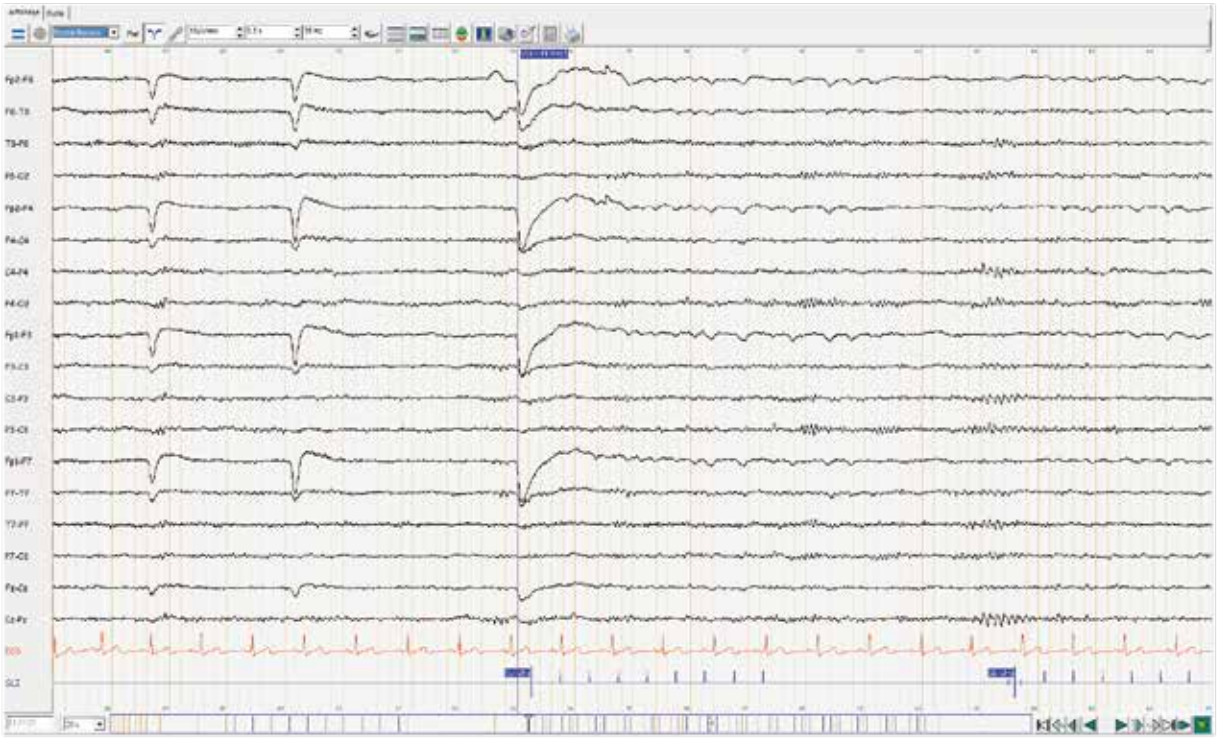

Figure 1. 19 y.o. patient with a first unprovoked generalized seizure during wakefulness. Routine EEG was performed <24 hours of the episode. It showed a posterior background activity at 8Hz, bilateral, symmetric, reactive. Bipolar montage.

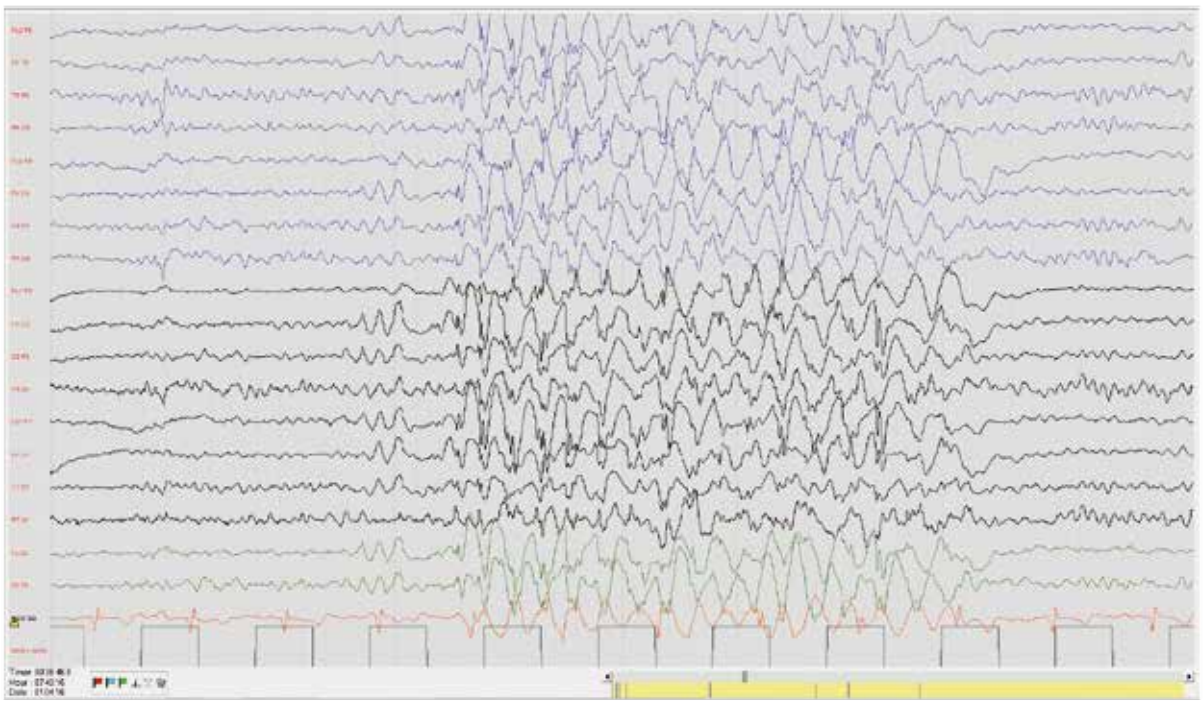

Figure 2. Same patient. Light sleep on awaking showed frequent bursts of 4 Hz generalized spike-poly-spike wave-complexes, of variable length, without clinical correlates. Bipolar montage.

4. Relevance of ictal recordings in the 1st EEG

It is possible that the first seizure which comes to medical attention, is not the patient's true first seizure [9, 23]. Patients presenting at emergency often have a history of more subtle seizures (e.g., absence seizures or myoclonic or simple partial seizures) that were not identified by the patient or its entourage. These types of seizures could be observed already during the first routine EEG. For this reason the facilitating techniques are fundamental during EEG: for instance, hyperventilation can trigger absences in children with untreated childhood or juvenile absence epilepsy; photic stimulation can induce myoclonic jerks in patients with juvenile myoclonic epilepsy. Focal seizures occur more rarely during standard EEG, and if they do, they are rather an alarming sign for a very active epileptic condition and hospitalisation should be considered. In any case, individualized and specialized care and appropriate antiepileptic medication should be initiated. If the routine EEG shows an electrical, or non-convulsive, status epilepticus, injection of antiepileptic drugs under EEG control and hospitalisation is strongly recommended.

5. Risk of relapse

In 2014, a meta-analysis estimated the risk of relapse after the first event in patients who were treated immediately or with delay and showed a risk of 15%, 8%, 6% and 7% of relapses after 6, 12, 18 and 24 months in patients who were treated immediately. If an observational attitude was chosen and treatment postponed, these numbers increased to 18%, 10%, 9% and 7%. The risk of relapse was higher in patients with an abnormal EEG than with an abnormal imaging, given that not all epilepsy syndromes are related to cerebral lesions [24]. Several studies with long follow-up showed that 80 to 90% of individuals recur within two years of the initial seizure [25].

However, while early antiepileptic treatment decreased the number of further seizures, it did not change relapse rate beyond 2 years disease duration. Indeed the two multi-centre randomized trials (FirST, MESS) failed to show any change in long-term prognosis in patients with early treatment versus delayed treatment after further seizures [26].

EEG and brain imaging are considered essential as part of the neuro-diagnostic evaluation of adults presenting with an apparently unprovoked first seizure, as suggested by the practice parameter from the American Academy of Neurology [27]. A prospective study on 208 consecutive patients with first seizure followed for 5 years [28], showed that an EEG with epileptiform abnormalities was associated with a relative increase for seizure recurrence at 1 to 5 years of 2.16 (95% CI 1.07 - 4.38) as compared to patients without such EEG abnormalities. It is important to remember that the EA presence in healthy subjects is extremely rare, with an incidence of 0.5% [29].

Although interictal EA have been associated with a higher risk of relapse [1, 30 - 32] their diagnostic value has been unclear for a long time. Indeed a meta-analysis of 2003 [32] showed that sensitivity and specificity of interictal EA for seizure relapse after a first seizure varies widely among published studies, with a range from 20% to 80% for sensitivity, and 41% to 99% for specificity. Just recently, a Cochrane [33] systematic review and meta-analysis about diagnostic accuracy of routine EEG on 1799 patients with first seizure and 1 year of follow-up was published [34]. In adults, sensitivity (defined as the percentage of EEG with EA, when epilepsy is present) is 17.3% (range 7.9 - 33.8) and specificity (percentage of presence of epilepsy, when EEG shows EA) is on average 94.7% (range 73.7 - 99.1). In children, a sensitivity value of 58 % (range 49.7 - 65.6) and a specificity of 70% (range 57.5 - 79.5) were identified. The same study revealed that an adult presenting with a first unprovoked seizure has a 77% post-test probability of relapse if routine EEG includes EA (positive likelihood ratio) and 47% if it does not (negative likelihood ratio). Similary, a child has a 66% post-test probability of relapse if routine EEG includes EA and 38% if it does not. These observations are extremely important, considering that a patient with a first unprovoked seizure should be treated if the probability of relapse is >60% at 10 years [6].

Other factors carry important information regarding the overall prognosis, as the underlying syndrome. Idiopathic generalized (or genetic generalized, as it is named in the new classification) epilepsy achieves remission in 80 to 85% compared to focal epilepsy in 40 - 65% [3]. Multiple seizure types in the same patient are associated with higher seizure recurrence [26]. Younger age at onset has also been described as predictor of worse outcome. Onset of epilepsy before the age of 12 months is a poor prognostic factor. Best prognosis is noted if onset occurs after the age of three years [25]. A prospective observational study of over 1000 adults presenting with a first unprovoked seizure showed a similar likelihood of seizure recurrence in older (> 65 years) compared with younger adults (53 versus 48 percent). However, by five years, the cumulative risk of recurrence was higher in older adults (75 versus 61 percent). This relates to a greater likelihood of a remote symptomatic etiology rather than age itself [35]. Another powerful predictor of the long-term prognosis is the early response to treatment. Several studies found that the response to the first antiepileptic drug showed to be the strongest predictor of good long-term outcome in adults and children. Along the same line, patients who are not seizure-free after ≥ 2 antiepileptic drugs should be referred to specialized centre to determine the reasons for lack of response and/or search for the possibility of epilepsy surgery [36].

Recently, Fisch et al. showed that patients with installed medical follow-up are significantly more likely to receive a precise diagnosis and increased delay to the next unprovoked seizure in comparison with patients without organized medical care (p=0.008). The study emphasized the need of specialized care starting already in the emergency room, provided by epileptologists. After a first evaluation, important exams such as EEG and MRI are rapidly and reliably scheduled and results can be discussed at the next appointment. Early-specialized improved not only the diagnostic accuracy, but also adherence to follow-up consultations, probably because patients better understood their condition and the importance of compliance and lifestyle adjustments [37].

Psychiatric and neuropsychological comorbidities are associated with a lower response to drug treatment and higher risk of failure of remission. In these cases, specialized consultations, relevant non-epileptic treatment and/or increased frequency of follow-up appointments should be scheduled, at least initially [38, 39].

To conclude, EEG is a fundamental test to diagnose the presence or absence of epilepsy after a first seizure. Ideally, it should be performed as fast as possible after the event, if possible within 24 hours. Proper and correct diagnosis of the type of epilepsy is fundamental in order to offer optimal treatment and prognostic information regarding seizure relapse. It is self-evident that such information is of utmost importance for the medical and socio-professional wellbeing of each patient. It should not be forgotten that with each initiation of treatment the possibility and timing of withdrawal of antiepileptic medication should be discussed with the patient, if possible early in the course of the disease to avoid "autonomous" withdrawals which end in the emergency room.

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