Abstract

Background: The Electroencephalogram (EEG) is the gold standard technique to assess the epileptogenic cortical activity. However, due to the neurophysiology of the bioelectrical signal and the short duration of the routine EEG (rEEG) and sleep-deprived EEG (sEEG) registers, the sensitivity is low. The 24-hour Ambulatory EEG (aEEG), being a prolonged recording, could significantly improve the diagnostic capability, in an attractive cost-effective way. In this study, we analyzed the aEEG of patients with suspected epilepsy, addressing its specificity and sensitivity for the clinical diagnosis of epilepsy. Additionally, we endeavour to ascertain any other possible predictive factors of diagnosis.

Methods and Findings: Retrospective observational study enrolling consecutive patients with suspected epilepsy who underwent aEEG between May 2011 and May 2018 at the Neurophysiology Laboratory from Local Health Unit of Matosinhos – Pedro Hispano Hospital. A sample of 83 individuals was obtained, with a mean age of 44.5 years (79 adults and 4 paediatric). aEEG showed a good diagnostic capacity for the clinical diagnosis of epilepsy with a specificity of 97% and sensitivity of 68%. The rate of false-negatives and false-positives was 7% and 5%, respectively. It’s expected that patients with an indication of syncope or loss of consciousness will not have epilepsy diagnosis.

Conclusion: The aEEG can be a useful tool to assess patients with suspected epilepsy and unremarkable routine and sleep-deprived EEGs, or in cases of suspected non-epileptic seizures, particularly to exclude the epilepsy diagnosis given its high specificity. This approach can lessen the time required to identify the diagnosis.

Keywords: Epilepsy; Diagnosis; Electroencephalogram; Sensitivity

Introduction

The rEEG is the first-line exam for the diagnosis of epilepsy, however, its sensitivity is low (30-50%) [1], mainly due to its reduced registration time and the biophysics of the cortical neurophysiological signal. The sensitivity can be increased to 60-70% with the repetition of rEEG, or to 54-84% with a sEEG after a normal rEEG [1]. Nonetheless, aEEG is still capable of recording epileptiform activity (EA) in a considerable proportion of cases with normal rEEGs and/or sEEGs [2]. Thus, it is expectable that the problem of continuously repeating rEEG and/or sEEG to increase the sensitivity, which also increases the time to diagnosis and augments cost [3], could be at least partially solved with the use of aEEG in selected cases [4,5].

The aEEG is known for its favorable cost-effectiveness profile. Its cost is 51-65% lower than for 24-hour inpatient admission for VEEG monitoring [6]. Besides this, recently, in Portugal, Borges DF et al. estimated that epilepsy diagnosis through aEEG is 1.8 times more expensive than with sEEG, which economically justifies the use of the first one instead of the repetition of the second one, being the first unremarkable [7].

The International League against Epilepsy (ILAE) guidelines of 2018 recommends a rEEG (with the duration of at least 20 minutes and with activation tests) as the first approach to a seizure [8]. When
rEEG results are inconclusive, the recommended approach is sEEG [8]. If the diagnosis remains unclear, in specific cases, especially if a specific trigger is suspected, aEEG should be considered [8]. This leads to the assumption that aEEG nowadays is underused and undervalued in standard clinical practice.

Especially knowing that the rate of misdiagnosis in epilepsy is about 20% [9], further clinical studies are needed to determine the relevance of aEEG in epilepsy diagnosis. Therefore, in this study, the main purpose is to assess the diagnostic capacity of the aEEG in patients with suspected epilepsy, thus contributing to the optimization of clinical practice in Epileptology.

Research Methodology

This is an observational retrospective study that included consecutive patients who underwent aEEG between May 2011 and May 2018 at Pedro Hispano Hospital Neurophysiology Laboratory, requested by an Epileptologist, for clinical suspicion of epilepsy, hence without a confirmed diagnosis and with previous normal rEEG/sEEG.

If rEEG and sEEG has a low sensitivity mainly due to its short duration as described in the literature, being the aEEG a long term monitoring method, it’s expected that its impact in the clinical diagnosis of epilepsy to be of irrefutable importance in clinical practice when compared or associated with these exams. So, the primary objective was to analyze the specificity and sensitivity of this test for the clinical diagnosis of epilepsy, and the secondary objectives were: (a) to evaluate if there is a relationship between the presence of epileptiform activity (EA) and the presence of lesion ascertained by Cranial Magnetic Resonance Imaging (cMRI); (b) to evaluate patients’ follow-up through consultation of the clinical records after the recording of the aEEG to determine if the diagnosis - positive or negative for epilepsy- made by the Epileptologist at that time was preserved or changed; and (c) to weigh the determinants of aEEG diagnosis.

The positivity or negativity of the aEEG was attributed according to the presence or absence of EA during the recording, respectively, e.g. spikes, sharp waves, polyspike complexes, spike-and-slow-wave complexes, and spike-wave complexes. The slow activity (SA) was not considered a positivity factor for aEEG, since it is an indication of focal brain dysfunction, especially in waking adults, and appears to be the result of a de-stressing of subcortical structures [10].

The gold standard for the diagnosis of epilepsy, which was used to calculate the specificity and sensitivity of the aEEG, was the clinical diagnosis made by the Epileptologist, according to the ILAE definition and criteria at the time of the first appointment immediately after the aEEG [8].

To perform the aEEG, a Headbox Micromed® SD LTM32 BS was used with a 2 GB SD memory card. Grass® electrodes with 152 cm gold disc were applied based on the International System (IS) 10/20 with 6 additional electrodes (F9/F10, T9/T10, P9/ P10) according to IFCN recommendations [11], the ground electrode (G1) positioned in FCz and the reference electrode (G2) positioned in CPz and, additionally, a lead for electrocardiogram (ECG) recording was used. The impedances were set below 5 Kohms and a sampling rate of 256 Hz was used at acquisition. After the electrode placement was carried out, a recording of about 5 minutes was made to evaluate the signal quality, filters applied, impedances and the detection and correction of relevant artifacts. The duration of the recording was at least 24 hours, during which a synchronized video system was not used. However, an event diary was provided for patients or witnesses to catalog the perceived events, marking the time and a description of the event. This enabled a more informed interpretation of the EEG trace during their analysis.

The aEEG analysis and report were performed entirely and solely by visual inspection of an experienced Clinical Neurophysiologist using System Plus software initially, and later System Plus Evolution (Micromed, Treviso, Italy), after an upgrade.

This study was approved by the Competent Ethics Committee (CEC) and the Board of Directors of the Pedro Hispano Hospital. Data manipulation was made strictly according to the approval of the CEC, and the confidentiality and anonymity of the information related to the patients’ private data were guaranteed.

Statistical analysis

Data was compiled and checked for quality control, after which it was imported to SPSS Statistics version 24 (IBM, Armonk, NY) for statistical analysis. The distribution of variables was tested for normality by the Shapiro-Wilks test. A simple descriptive statistic method was applied for demographic and clinical characterization. Data are presented as mean ± standard deviation (SD) for continuous variables, and as frequency (%) for categorical variables. Sensitivity, specificity, rate of true and false-positives, rate of true and false-negatives, and diagnostic accuracy of the aEEG was estimated with the Open Epitool [12], and confidence intervals were adjusted according to the Simpson’s method. The receiver operating characteristic (ROC) curve was used to check the overall performance of the aEEG based on the estimation of the area under the ROC curve (AUC). A simple univariable logistic regression analysis was performed to identify the determinants of clinical diagnosis of epilepsy. A 2-tailed p<0.05 was considered significant. 95% confidence intervals (CI) were also considered in the analysis.

Results

Demographic and clinical characterization of the population

The present study included 83 patients, 46 female, and 37 male subjects, 79 adults and 4 paediatric patients (age range: 7-84 years) with a mean age of 44.5 years (Table 1). In the analysis of the clinical information available, the type of suspected epilepsy was categorized at the outset. Thus, focal epilepsy was suspected in 32 (39%) of the patients, generalized epilepsy in 10 (12%) and undetermined epilepsy or undetermined events in 41 (49%). Concerning anti-epileptic drugs (AED), 49 (59%) patients were untreated, 29 (34%) were under 1 AED and 6 (7%) patients received 2 AEDs.
The patients were subjected to the following indications: a) suspicion of a specific type of epilepsy (68%); b) events of collapse, syncope or loss of consciousness (LOC) (18%); c) differential diagnosis of seizures and non epileptic events (8%); d) other alterations (6%) such as mesial temporal sclerosis and other changes in RMce.

Regarding the neurophysiological investigation before the aEEG, more specifically the rEEG and the sEEG recordings performed, it was estimated that, on average, the individuals performed a total of 1.6 EEG (routine and/or sleep deprivation). The mean duration of the rEEG and sEEG performed before aEEG was 65 minutes with a range of 20 to 257 minutes for a total of 68 patients. 56 (68%) underwent one rEEG/sEEG, 15 (18%) performed two, 5 (6%) performed three, 2 (2%) four, 3 (4%) five and 2 (2%) six. Regarding rEEG 25 (30%) patients did not test this, whilst the remaining 58 (70%) underwent either one (45; 54%), two (10;12%), three (1; 1%), or five (2; 2%) rEEG. In the case of sEEG, 42 (51%) of the patients did not perform this test, 32 (39%) underwent one, 6 (7%) performed two, 1 (1%) performed three sEEG, and 2 patients (2%) had a total of foursEEGs.

Concerning the aEEG results, the mean duration was 24.07 hours (24.0 – 27.5 hours), of which 30 (36%) were positive and 53 (64%) were negative. Electroencephalographic findings (EA and SA) were found in 33 (40%) individuals, of whom 18 (22%) EA and 12 (15%) focal SA and EA, and 3 (4%) were focal SA. Two patients (2%) had epileptic seizures during recording and 10 (12%) presented non-epileptic events (Table 1).

Of the electroencephalographic changes observed in the aEEG (EA and SA), assuming n=33, all of them were identified as focal activity, of which 5 (15%) patients had pathological activity restricted to the frontal lobe, 25 (75%) patients in the temporal lobe, whilst 2 (6%) patients had occipital dysfunction and 1 (3%) patient had multifocal pathological activity. Figure 1 represents an example of a EA, showing low voltage spikes over the right centropetal temporal area. To evaluate if there was a relationship between the presence of EA and the presence of a lesion, the topography, and etiology of the lesions visualized in cMRI were also assessed. The types of etiologies found were hemorrhagic, traumatic, mesial temporal sclerosis, vascular, metabolic, hippocampal asymmetry, iatrogenic and tumoral. Only 22 patients with previous cMRI had a non-normal result. It was found that 18 (82%) had a focal lesion while the rest 4 patients (18%) presented multifocal lesions. Of the 22 patients with lesion visualized in cMRI, interictal activity was recorded in 11 individuals. In 6 patients (55%) the location of the interictal activity and the lesion were coincident, in 4 of these patients the interictal activity was EA and in 1 it was SA. It should also be noted that 4 of the 6 patients (36%) patients had temporal lobe topography (3 right and 1 left).

The inquiry in the first appointment after the aEEG revealed that 44 (53%) patients had a clinical diagnosis of epilepsy at that time. Within a year or approximately a year after the aEEG 46 (57%) had a diagnosis of epilepsy. In the maximum available follow-up period (last existing clinical appointment after the aEEG) 45 (56%) were diagnosed with an epilepsy diagnosis. In the last two moments referred to only 81 individuals were counted, since two of the sample individuals did not continue to be followed at the Pedro Hispano Hospital.

Impact of aEEG in epilepsy clinical diagnosis

In the first place, it should be noted that the technical conditions during the acquisition remained good and the occurrence of artifacts didn’t hinder the recording nor the legibility and interpretation of the exam.

The estimated specificity of the aEEG in the diagnosis of epilepsy was 97.4% (CI: 86.8, 99.5), while the sensitivity was 68.2% (CI: 53.4, 80.0). Positive and negative predictive values were 96.8% (CI: 83.8, 99.4) and 73% (CI: 59.8, 83.2), respectively. The calculated diagnostic accuracy of the aEEG was 81.9% (CI: 72.3, 88.7) (Table 2).

The ROC curve analysis (Figure 2) to determine the diagnostic capacity of the aEEG for epilepsy provided an area of the curve (AUC) of 0.83 (CI, 0.74, 0.92; p<0.0001).

Figure 3 represents the STARD diagram [13], in which the diagnostic accuracy of the aEEG is represented; it is possible to admit that 97% of the individuals with detected EA were diagnosed with epilepsy, and that of the records without EA, 26% were diagnosed with epilepsy.

Regarding the changes in the clinical diagnosis of epilepsy and admitting a sample size of 81, it was verified that in cases where the diagnosis was negative for epilepsy after the aEEG, 31 (82%) remained unchanged within a year, and in the maximum follow-up period, 32 (84%) had no clinical diagnosis of epilepsy. Of the cases with a positive diagnosis for epilepsy after aEEG, 39 (91%) remained unchanged and 4 (9%) no longer had a clinical diagnosis of epilepsy at the two recorded moments (Table 3). All these changes in the clinical diagnosis were made by the Epileptologist since it is the gold standard for epilepsy diagnosis, according to all collected clinical evidence at that time and the ILAE epilepsy definition [8].
Figure 1  EEG traces using the 25-channel configuration showing EA (low voltage spikes) over right centrottemporal area (Comprising C4 and T4 electrodes).

Table 2 Sensibility, specificity, PPV, NPV and diagnostic accuracy of the aEEG.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>97.40%</td>
<td>86.8, 99.6</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>68.20%</td>
<td>53.4, 80.0</td>
</tr>
<tr>
<td>Positive Predictive Value (PPV)</td>
<td>96.80%</td>
<td>83.8, 99.4</td>
</tr>
<tr>
<td>Negative Predictive Value (NPV)</td>
<td>73.10%</td>
<td>59.8, 83.2</td>
</tr>
<tr>
<td>Diagnostic Accuracy</td>
<td>81.9%</td>
<td>72.3, 88.7</td>
</tr>
</tbody>
</table>

Figure 2  ROC curve of the aEEG.
Table 3 Changes in the clinical diagnosis of epilepsy up to 1 year after the aEEG and in the maximum follow up period.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Negative clinical diagnosis for epilepsy after aEEG</th>
<th>Positive clinical diagnosis for epilepsy after aEEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up up to 1 year after the aEEG</td>
<td>No changes up to 1 year, N (%) 31 (82%)</td>
<td>No changes up to 1 year, N (%) 39 (91%)</td>
</tr>
<tr>
<td></td>
<td>With changes up to 1 year, N (%) 7 (18%)</td>
<td>With changes up to 1 year, N (%) 4 (9%)</td>
</tr>
<tr>
<td>Follow-up the maximum follow up period</td>
<td>No changes in the maximum follow up period, N (%) 32 (84%)</td>
<td>No changes in the maximum follow up period, N (%) 39 (91%)</td>
</tr>
<tr>
<td></td>
<td>With changes in the maximum follow up period, N (%) 6 (16%)</td>
<td>With changes in the maximum follow up period, N (%) 4 (9%)</td>
</tr>
</tbody>
</table>

Through the follow-up of the individuals, it was calculated the rate of false- negatives and false-positives of the clinical diagnosis as a function of the aEEG, which was 7% (6 individuals) and 5% (4 individuals), respectively. In both false- negatives and false-positives, the diagnosis was changed within one year by the Epileptologist.

Regarding the presence and type of interictal activity in the aEEG and the presence of a lesion in cMRI, of the individuals with the presence of a lesion in cMRI, in 11 (50%) no interictal activity was detected in the aEEG, in 1 (5%) SA was detected, in 10 (42%) EA, and in 3 (14%) SA and EA were detected. From these 11 cases, in 6 (55%), the location of the EA and the lesion overlapped topographically.

Through a logistic regression analysis to find determinants of the diagnosis, the following results were obtained: a) the relationship between the “aEEG indication” variable (for collapse/LOC versus epilepsy) and the “clinical diagnosis after aEEG” variable resulted in an odds ratio (OR) of 0.255 (95% CI, 0.074, 0.881, p<0.05); b) the relation between the variables “indication for aEEG of suspected epilepsy” and “clinical diagnosis after aEEG”, an OR of 2.627 (95% CI, 1.019, 6.776, p<0.05) was obtained.
Discussion

In the present study, the results showed that the aEEG has a good diagnostic capacity for epilepsy with a specificity of 97% and a sensitivity of 68%. aEEG allowed the diagnosis of epilepsy in 53% of the patients when rEEG and/or sEEG were not able to do so. These results support the importance of the aEEG as a fundamental complement for the diagnosis of epilepsy, supporting its adoption as a crucial second-line examination in patients with suspected epilepsy with a negative initial neurophysiological study. This seems to be fundamentally related to the longer duration of this EEG modality comparing to rEEG and sEEG. The results here presented support the ILAE indications regarding the use of this diagnostic method and its efficiency in clinical practice. Currently, in clinical practice, this study contributes to abolish the global underutilization of aEEG.

These results show better specificity and sensitivity than the prospective study done by Keezer et al. in 2015, which obtained a sensitivity of 58% and a specificity of 95.5% for the clinical diagnosis of epilepsy. However, contrary to the present study, the sample of Keezer et al. consisted not only of individuals with suspected epilepsy but also with a previous diagnosis of epilepsy [5]. A possible reason for this difference might be the use of the inferior temporal additional electrodes in this study, given that the temporal lobe is the most frequent source of EA in adults [11].

Regarding the secondary objectives, the rate of false-negatives and false-positives was 7% and 5%, respectively. Of the 6 patients with false-negative results in the aEEG, 5 of them were under AED therapy, which may have been the major influence and cause for the test result. There are no data, as far as we know, in the literature that could support or contradict our results regarding the rate of false-positives and false-negatives, which is one of the reasons why it’s imperative that further researches are made.

Concerning the presence of EA in the electroencephalographic record and the presence of a lesion in cMRI, no relationship was found between these two variables, contrary to what was found by Siddiqi et al. who confirmed that the presence of a brain injury in cMRI is associated with a higher rate of EA detection [14]. This result is probably due to the fact that the total number of individuals with lesions seen in cMRI was only 22 patients, limiting the establishment of a relationship between the variables due to low statistical power.

For the results obtained in the logistic regression, it can be expected that most patients indicated to perform aEEG by collapse/LOC episodes are normally not diagnosed with epilepsy. This also happens in patients with suspected epilepsy, who are 2.6 times more likely to present a clinical diagnosis of epilepsy. According to Pournazari et al. in a study on the impact of neurological tests in the diagnosis of syncope, although recurrence to these methods is very frequent, its diagnostic utility is significantly low [15]. Therefore, and in accordance with our results, it seems that the use of this technique in the differential diagnosis of collapse or LOC episodes is not recommended.

The study has some limitations that predictably must be considered. The sample size is one of the main limitations, particularly in the sub-group analysis where the small number of cases conditioned low statistical power. The present study is also limited by its retrospective nature, which affects the type and diversity of the sample selected and increases the risk of relevant bias and confounding factors due to lack of relevant information or inaccuracies in the clinical records of the patients. Also, there were some inherent limitations of the aEEG recording technique, such as the fact that only 59% of the subjects were without antiepileptic drugs (AED) at the time of the examination, and also the fact of being a non supervised exam. It is acknowledged that AED can influence the results of the EEG, however, this reflects clinical options, regarding other non-neurophysiological risk factors for recurrence of seizures (e.g. clinical and imaging factors) [16].

Few studies have assessed the impact of aEEG in patients with suspected epilepsy comparing to other EEG modalities, especially in Portugal, where this question was never published. Further studies in an adult population with suspected epilepsy are needed to answer and justify the questions raised in this study because this represents an essential future research direction in Clinical Neurophysiology field.

Conclusion

This study shows the importance of aEEG as a complementary diagnostic method in cases of suspected epilepsy proving that it is ancillary in the clinical diagnosis when the previous studies (rEEG and/or sEEG) are inconclusive. The aEEG should be considered more frequently and earlier in clinical practice according to the ILAE recommendations instead of repeating rEEG or sEEG indefinitely as ensued in some of the cases presented in this study. Its use can clarify the positivity or negativity of the clinical diagnosis of epilepsy in cases of suspicion, given its high diagnostic rate in complementarity with the other diagnostic techniques, and its greatest benefit lies within its high specificity akin to its particular cost-effectiveness profile, allowing greater efficiency, speed and lower cost excluding the epilepsy diagnosis.

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