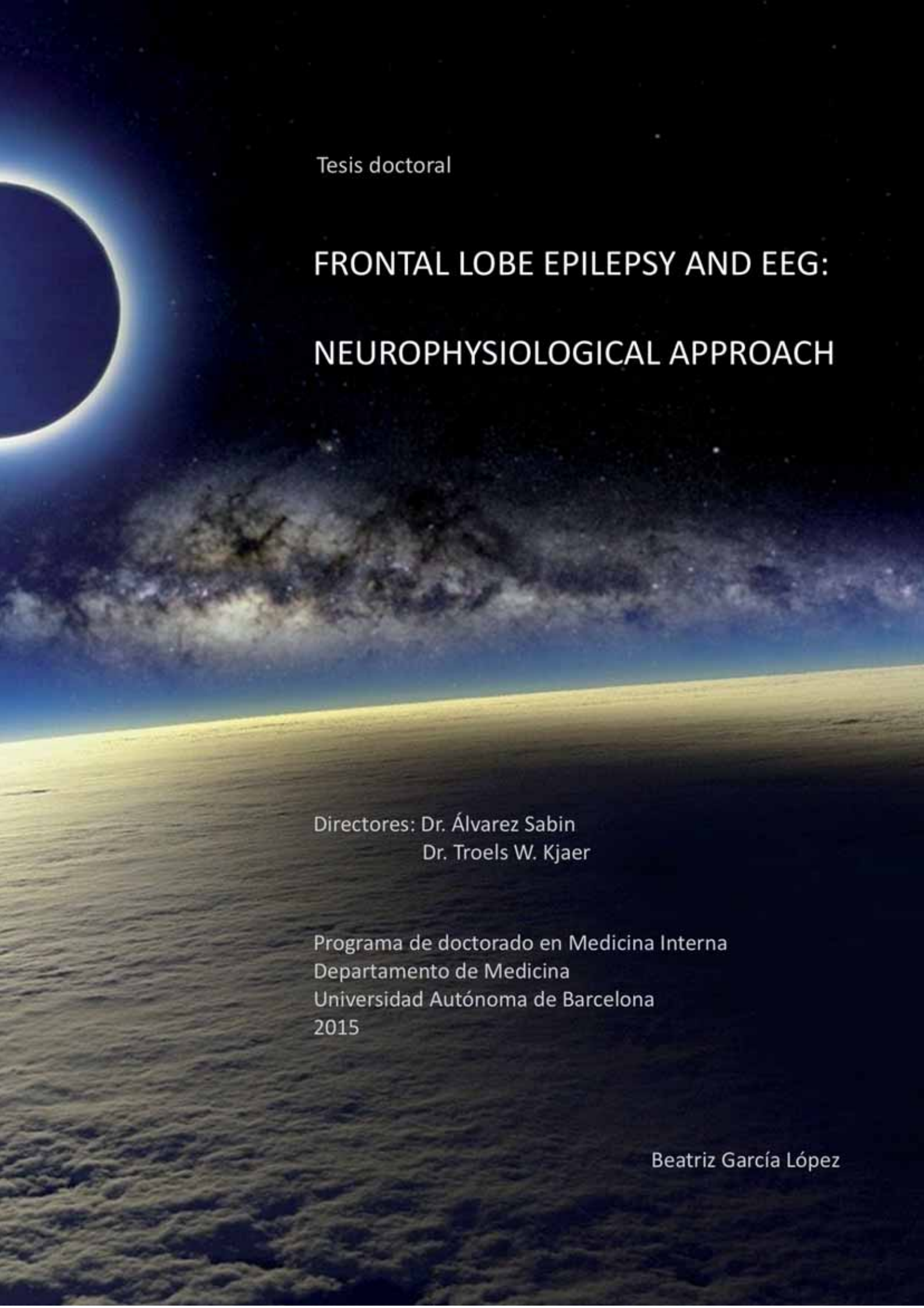

Tesis doctoral

FRONTAL LOBE EPILEPSY AND EEG:

NEUROPHYSIOLOGICAL APPROACH

Directores: Dr. Álvarez Sabin
Dr. Troels W. Kjaer

Programa de doctorado en Medicina Interna
Departamento de Medicina
Universidad Autónoma de Barcelona
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Beatriz García López

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ABSTRACT

1. ABSTRACT

Frontal lobe epilepsy (FLE) is the second most common type of epilepsy after temporal lobe one. Clinical and electroencephalographic (EEG) features are also very varied, being its diagnose usually a challenge in clinical practice. Frontal lobe seizures appear frequently in cluster, with secondary generalization, and its EEG appearance is usually difficult to determine, due to the widespread the interictal and ictal activity usually achieves.

This is an electroencephalographic study, where 175 cases with frontal lobe EEG interictal epileptiform activity have been carefully studied regarding an electroencephalographic point of view, with special emphasis in the morphology of the waveforms. Regarding the ictal activity, some morphologic details at onset are studied with the aim to make available a practical EEG classification for these seizures.

A major point of interest of this work is included in the graphical appendix, where some interesting EEG features are detailed.

RESUMEN

La epilepsia del lóbulo frontal es la segunda más frecuente en la mayoría de las series publicadas, después de la epilepsia temporal. Sus características clínicas y electroencefalográficas son muy variadas, lo que hace de su diagnóstico y tratamiento un reto en la práctica clínica.

Las crisis frontales suelen aparecer en “clusters”, con frecuencia generalizan y el aspecto electroencefalográfico de la actividad intercrítica y crítica suele ser difícil de interpretar por la gran difusión que suele acompañar a la actividad paroxística en este tipo de epilepsia.

En este trabajo se han estudiado 175 casos con alteraciones intercríticas en el electroencefalograma, realizando un análisis exhaustivo de todos sus aspectos morfológicos. En cuanto a la actividad crítica se han estudiado en detalle sus características morfológicas al inicio de la crisis y sus frecuencias, con el propósito de disponer de una clasificación útil desde el punto de vista electroencefalográfico en el estudio de este tipo de epilepsias.

Una parte fundamental del trabajo se encuentra en el anexo incluido a modo de “atlas”, en el que se exponen algunos de los casos objeto de estudio, detallando observaciones electroencefalográficas de interés.

ABREVIATIONS

2. ABREVIATIONS

- FLE: frontal lobe epilepsy
- EEG: electroencephalogram or related to it.
- IED: Interictal epileptiform discharges
- EMU: Epilepsy monitoring unit
- ANT: Anterior
- POST: Posterior
- MTLS: Mesial temporal lobe seizures
- TLE: Temporal lobe epilepsy
- AED: Antiepileptic drugs
- MRI: Magnetic resonance imaging
- TBI: Traumatic brain injury
- CT: Computerized tomography
- CVA: Cerebrovascular accident

INTRODUCTION

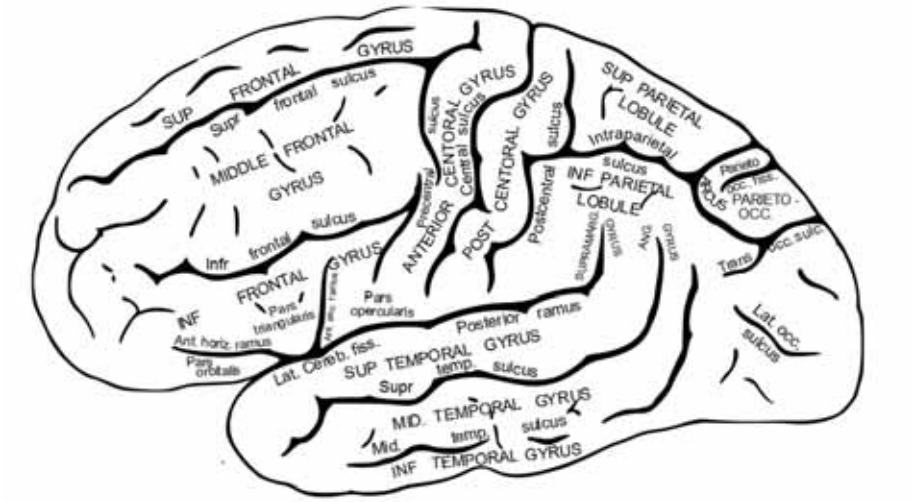
3. INTRODUCTION

This study focuses on the morphology aspects of electroencephalography in frontal lobe epilepsy. A comprehensive morphological analyses of the epileptiform activity, both interictal and ictal, is performed.

3.1 BRIEF INTRODUCTION TO ANATOMY AND HISTOLOGY OF FRONTAL LOBE

The frontal lobes are located in the anterior region of each of the two cerebral hemispheres. They can be divided in different regions regarding different criteria: anatomically by sulcus that delimitate gyrus, histologically by cytoarchitecture and functionality.

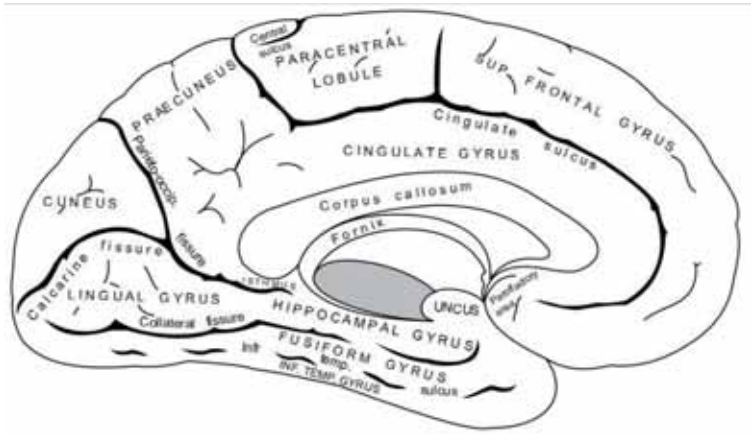
Anatomically, the frontal lobes are delimited between lateral sulcus (Silvio sulcus) and Central sulcus (Rolando sulcus). Anterior and parallel to the central sulcus there is the pre-central sulcus, delimiting between them the pre-central gyrus. Anterior and perpendicularly to pre-central sulcus there are frontal superior and inferior sulcus, that delimitate anatomically from medial to lateral the superior, media and inferior frontal gyrus.



ANT. POST.

Fig. 1 Lateral surface of frontal lobe.

In the medial surface the frontal superior gyrus and the para-central lobule are above the cingulated gyrus.



POST. ANT.

Fig. 2 Medial surface of frontal lobe.

In the inferior surface of the frontal lobe there are from medial to lateral: the gyrus rectus, the olfactory sulcus and the orbital gyrus, divided into medial and lateral; the central part of the orbital gyrus is divided into anterior and posterior.

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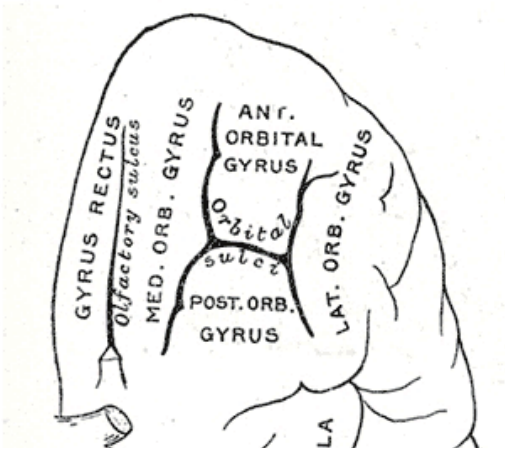


Fig. 3 Inferior surface of frontal lobe.

POST.

Histologically, the frontal lobe can be divided in regions by cytoarchitecture and functionality. The brain cortex has different type of cells: pyramidal cells, stellate, Cajal and Martinoti horizontal cells, neuroglia; their distribution in layers conform the cytoarchitecture of the cortex: I-molecular layer (plexiform), II-external granular layer, III-external pyramidal layer, IV internal granular layer, V, internal pyramidal layer, VI Polymorphic or multiform layer.

3.2 INTRODUCTION TO EEG RECORDING

EEG was first carried out on humans with electrodes placed on the front and back of the head[1]. As different laboratories tested the method, more electrodes at different points were used and a pattern distribution of the activity was observed.

[1]Hans Berger was the investigator who first successfully recorded EEG on humans, and described what he saw as a measure of global cortical activity, 1929.

[2]Chatrian et al., 1974; Herner, 1977.

[3]There have been also used soma montages derived from these. After the EEG channels breathing and ECG channels are added as complementary polygraphy.

4By definition the base of the spike is of 20 to 70ms, which ranges from 14,3 to 50 cycles/s.

[5]The high frequency filters round off the point crucial In the identification of a spike. Once rounded off,

The next steps were attempts to place electrodes in a standardized manner so that comparisons between patients and also within records of the same patient at different time could be made.

A committee of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology recommended a specific system of electrode placement for use in all laboratories under standard conditions, now known as the International 10-20 system.

In this system specific measurements from bony landmarks are used to determine the placement of electrodes, and to solve differences in head size it depends on proportions, using 10 or 20% of the previously specified distances. The standard numbering places odd-numbered electrodes on the left and even-numbered electrodes on the right, with a letter designating the anatomic region. "Z" refers to mid-line electrodes.

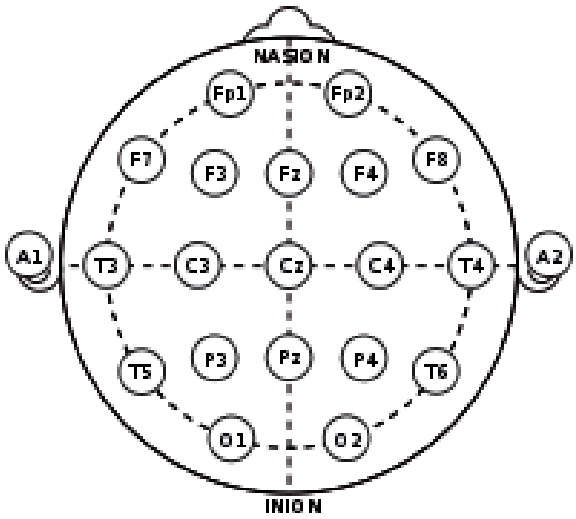


Fig. 4 International 10/20 system.

The term montage refers to the particular combination of electrodes examined at a particular point in time[2]. Multiple montages are used, depending on the characteristic of a specific recording, the preferences of the reader, the activity under study (Niedermeyer and Silva, 2005).

[2]Chatrian et al., 1974; Herner, 1977.

The montages are divided into two major categories: reference recording and bipolar recording.

In the reference recording the electrodes are all referred to one single electrode, one common electrode on each side of the head or the electrically combined activity from several electrodes. The most common reference variant used is the average montage, in which all the electrodes are combined as reference. This montage works well unless there is some transient voltage that is either very high or involves many electrodes.

In the bipolar variants one electrode is linked to other individual one, to demonstrate a marked change in polarity in the so-called phase reversal. This is useful to show the point of maximum deflexion with the change of polarity. If both electrodes are involved they cancel out, which complicates the reading in many cases. This makes necessary to use several bipolar montages and combine them with a reference montage for reading the recordings.

Montages[3]	Referential	Standard bipolar	Transversal bipolar	Longitudinal bipolar	Triangular bipolar	Circular bipolar
Channel 1	Fp1-Ave	Fp1-C3	Fp1-Fz	Fp1-F3	Cz-Fp1	Fp1-T3
Channel 2	Fp2-Ave	C3-T3	Fz-Fp2	F3-C3	Fp1-Fp2	T3-O1
Channel 3	F7-Ave	T3-O1	F7-F3	C3-P3	Fp2-Cz	O1-O2
Channel 4	F8-Ave	Fp2-C4	F3-Fz	P3-O1	Cz-F7	O2-T4
Channel 5	F3-Ave	C4-T4	Fz-F4	Fp2-F4	F7-F8	T4-Fp2
Channel 6	F4-Ave	T4-O2	F4-F8	F4-C4	F8-Cz	Fp1-F7
Channel 7	T3-Ave	T3-C3	T3-C3	C4-P4	Cz-F3	F7-T3

[3]There have been also used soma montages derived from these. After the EEG channels breathing and ECG channels are added as complementary polygraphy.

Channel 8	T4-Ave	C3-Cz	C3-Cz	Fz-Cz	F3-F4	T3-T5
Channel9	T5-Ave	Cz-C4	Cz-C4	Fp1-F7	F4-Cz	T5-O1
Channel 10	T6-Ave	C4-T4	C4-T4	F7-T3	Cz-T3	Fp2-F8
Channel 11	C3-Ave	Cz-T5	T5-P3	T3-T5	T3-T4	F8-T4
Channel 12	C4-Ave	T5-T6	P3-Pz	T5-O1	T4-Cz	T4-T6
Channel 13	P3-Ave	T6-Cz	Pz-P4	Fp2-F8	Cz-T5	T6-O2
Channel 14	P4-Ave	Cz-O1	P4-T6	F4-T4	T5-T6	Cz-C3
Channel 15	O1-Ave	Cz-O2	O1-Pz	T4-T6	T6-Cz	C3-C4
Channel 16	O2-Ave	O2-Cz	Pz-O2	T6-O2	Cz-O1	C4-Cz
Channel 17	Fz-Ave				O1-O2	
Channel 18	Cz-Ave				O2-Cz	
Channel 19	Pz-Ave					

Both low frequency and high-frequency filters are used for recording. Low frequency filters attenuate 20-30 % of a given frequency; at the other end of the frequency band there are high-frequency filters. It is critical that high-frequency filters are used in a way that they do not eliminate the wanted spike activity[4], and to take into account that they also affect the waveform[5].

Another aspect to be taken into account is the polarity of the waveforms. Each deflection of the signal indicates a change of voltage as a fluctuation of polarity due to changes in the electron availability. Every EEG channel has two inputs, and changes in

4By definition the base of the spike is of 20 to 70ms, which ranges from 14,3 to 50 cycles/s.

[5]The high frequency filters round off the point crucial In the identification of a spike. Once rounded off, it becomes difficult of differentiate a train of spikes from a train of beta waves.

each of them cause more available electrons (negativity) or less available electrons (positivity). It is worth noting that the EEG apparatus has been built according to one rule:

"Negativity of input 1: upward deflection; Positivity of input 1: downward deflection. Negativity of input 2: downward deflection; Positivity of input 2: upward deflection"

It should not be surprising that epileptic discharges may be absent on scalp recording since it is known that high voltage spike emanating from small regions of cortex may be markedly attenuated at the scalp (Goldensohn et al., 1970). Moreover, spike discharges may emanate from cortical regions distant from the convexity, sub-frontal or medial temporal cortex… being unrecorded at the surface.

3.3 FRONTAL LOBE EPILEPSY AND EEG

The frontal lobe epilepsy appears to be the second more frequent type of epilepsy[6] in most of the series, after temporal lobe epilepsy. But it is important to note that most of the studies are made of surgical series which may introduce some bias as less than 1% of patients undergo surgery due to epilepsy (Engel et al., 2007; Forcadas-Berdusan, 2002; Manford et al., 1996).

The frontal lobe epilepsy (FLE) is classified into six subtypes regarding the type of seizures[7] as proposed by the ILAE, but this classification is rather theoretical with a limited applicability in clinical practice, as there can be a mixture among the different types (Engel et al., 2007) and it is based on seizure location by post-surgical remission, which makes the patient group highly selected.

[6] At least in surgery centers, after temporal lobe epilepsy

[7] Focal clonic motor seizures, asymmetric tonic seizures, frontal lobe hyperkinetic, frontal lobe absence seizures, frontal opercular seizures and frontal lobe seizures that closely resemble typical mesial temporal lobe seizures (MTLs)

Any insult, lesion or primary genetic abnormality can be the etiological cause for the localization-related epileptic disorders classified by cerebral lobe. The site of the etiological lesion is the most critical for seizures expression (Jobst and Williamson, 2005; Manford et al., 1996)

Frontal lobe seizures can be easily misdiagnosed due to their broad types of clinical manifestations (Bauer et al., 2006; Engel et al., 2007). They often present during sleep, sometimes in cluster, frequently with early motor (Bagla and Skidmore, 2011) or with a variety of different clinical symptoms, none of them absolutely specific (Bagla and Skidmore, 2011) which contributes to its misdiagnose and makes them very difficult to classify clinically.

From an electroencephalographic point of view, interictal epileptiform abnormalities are said to appear in most patients with frontal lobe epilepsy (Beleza and Pinho, 2011)not confined only to frontal regions, even though other authors refer to the fact that the interictal EEG is usually normal, as well as ictal EEG,(12) so there are controversial and contradictory results in EEG studies of the frontal lobe epilepsy.

This work approaches the topic from an electroencephalographic point of view, as there are not many detailed electroencephalographic studies about EEG findings in frontal lobe epilepsy.

Beleza et al. are one of the few authors that have studied frontal lobe epilepsy regarding the location of the focus and its EEG expression. They divide frontal lobe epilepsy in three groups: dorsolateral frontal lobe epilepsy, mesial frontal epilepsy and basal frontal epilepsy (Beleza and Pinho, 2011). As Bagla R. et al, they find that interictal epileptiform abnormalities are presented in most patients with frontal lobe epilepsy, but they are usually not restricted to the frontal lobe (Bagla and Skidmore, 2011).

In the first type, dorsolateral frontal lobe epilepsy, there has been shown a bigger electroencephalographic concordance between a known lesion and the interictal EEG focal activity than in mesial frontal epilepsy (Vadlamudi et al., 2004). A possible reason for this difference is the smaller distance between the lateral cortex and the scalp

electrodes, as well as the fact that the dipoles tangential to the scalp in mesial FLE would made this problematic to be detected by EEG recording (Beleza and Pinho, 2011). "Repetitive epileptiform activity"[8] as ictal onset in lateral frontal lobe epilepsy (Foldvary et al., 2001) has been described as significantly more common than in mesial frontal lobe epilepsy, and rhythmic delta was found in 26% of the lateral frontal lobe epilepsy cases.

Basal frontal lobe epilepsy is described to have a regional distribution or appear more diffusely with bifrontal or front- polar maximum (Chang et al., 1991), and abnormalities detected by scalp EEG do not allow for topographic localization of foci residing in the basal frontal lobe, mostly due to the inaccessibility of the basal frontal surface to scalp electrodes (Beleza and Pinho, 2011). These foci can also show propagated epileptiform activity over central or front lateral regions, and may have a misleadingly widespread appearance because of the large distance and intervening cortical region that separates the focus from the scalp electrodes.

Mesial foci abnormal activity is described to appear in midline electrodes (Pedley et al., 1981), and some authors recommend transversal electrode setting including Fz, Cz, and Pz as an essential point in the EEG analysis (Blume and Oliver, 1996). Being the use of mid-line electrodes in those cases extremely necessary, as otherwise they find normal EEG recordings (Pedley et al., 1981).

Bautista RE. et al. found that the majority of patients with mesial frontal seizures have normal interictal and ictal surface recording (Bautista et al., 1998) but seizure patterns may still be evident at the vertex, where EMG activity is minimal (Beleza and Pinho, 2011). Foldvary et al. analysed seizures patterns and localization in partial epilepsy and found that "generalized patterns"[9] were observed in 45% of mesial frontal lobe

[8] "Repetitive epileptiform activity considered 3 or more discharges in sequence by authors.
[9] They considered "generalized patter" any activity involving multiple electrodes over both cerebral hemispheres having a less than 2:1 amplitude predominance of one side over the other.

epilepsy (Foldvary et al., 2001), and suppression[10] was also common in both frontal and mesial lobe epilepsy.

In the study of Foldvary et.al (Foldvary et al., 2001) none of the extra temporal seizures began with rhythmic temporal theta activity, and they consider this pattern as specific of mesial temporal lobe epilepsy (TLE). Beleza et al (Beleza et al., 2009) have found rhythmical midline theta in frontal lobe seizures, more frequently in FLE patients than in TLE patients. This rhythm was not observed in the control group of non-epileptic patients. So there seems to be a clear difference between location of rhythmic theta activity (temporal vs. midline) and the epileptic lobe (temporal vs. frontal) well defined by these two groups of authors.

Most of the studies do not focus on the morphology of the waves, and here is where the need of such a morphological study arises. Therefore, the main objective of this study is to provide a detailed morphological analysis of the frontal lobe epileptiform activity, both interictal and ictal. To achieve this goal the morphological aspects of the recordings will be carefully described to add a new and complementary view of the epileptiform activity in frontal lobe epilepsy.

[10] Suppression: activity ≤10 μV in amplitude (by authors).

OBJECTIVES

4. OBJECTIVES

The overall objective of this study is to describe the electroencephalography of frontal lobe epilepsy, as its diagnosis is often challenging due to the complexity of the EEG recordings. To reach this objective, a sample of EEG recordings of 175 cases of frontal lobe epilepsy is collected and reviewed. The primary objective is to provide a morphologic description of the interictal and ictal FLE activity, propose a new classification for frontal lobe seizures and discuss the most interesting EEG recordings. Secondary objectives cover the study of the possible association between different variables of interest, as well as the testing of some of pre-specified hypotheses.

4.1 PRIMARY OBJECTIVE: Morphological analyses of epileptiform activity

The primary objective of this study is to provide a morphologic description of the frontal lobe interictal and ictal epileptiform activity, propose a new EEG classification regarding morphology at seizure onset and discuss selected frontal lobe epilepsy EEG recordings with special attention to the morphology of the waves.

This is a new way of looking into frontal lobe EEG recordings, as to our knowledge there are not other similar studies on the topic. We hope this study will add to the current neurophysiological knowledge of the frontal lobe epilepsy, helping physicians to make the right EEG readings and facilitating the identification of frontal seizures. This is of special interest in frontal lobe cases due to the great diffusion that the activity usually presents, making the morphological details crucial to differentiate these cases from generalized ones.

In order to obtain meaningful results for the clinical practice focussing on its applicability in cases of frontal lobe epilepsy, the sample will be grouped by several aspects of its EEG morphology. First of all the morphological aspect of the interictal

activity will be studied regarding three axes and afterwards, the most relevant EEG morphological characteristics of the seizures will be described and a new morphological classification proposed. Selected recordings will be discussed with special emphasis on different electroencephalographic details as location, diffusion of the interictal activity, morphological characteristics at seizure onset, study of the variability of morphological seizure patter along time, differences depending on the electrode settings used, and any other detail of the specific cases presented, which will be individually considered.

Due to the fact that frontal lobe seizures are often confusing at its onset, given the extremely fast diffusion the ictal activity can achieve, an in-depth description of the waves' morphology at onset of the recorded seizures is also presented.

In order to help in the differentiation of the frontal focal interictal activity from ictal generalized activity in cases with high diffusion, along with the above specified morphological description, emphasis is placed on the differentiation between interictal and ictal EEG activity. Through the detailed analysis of the most interesting cases of the sample, some useful clues are expected to be identified for its application on clinical practice to avoid the misinterpretation of interictal frontal activity as ictal instead.

4.2 SECONDARY OBJECTIVES

The secondary objectives cover the study of the possible association between different variables of interest, as well as the testing of some of pre-specified hypotheses.

4.2.1 Hypothesis testing: Location and morphology of seizure pattern remains the same over time for each patient

This hypothesis is based on clinical experience following the impression that the ictal activity for a patient maintains the main morphological aspect and location of onset over time, although there might be changes in the duration, amplitude or even cortical diffusion and subsequent differences in their clinical manifestations. The confirmation of this hypothesis would imply that once the ictal activity for a patient is recorded, that information could be maximised in subsequent contacts.

To test this hypothesis, the subgroup of patients with at least two registered seizures will be selected. For those patients, the location at onset and morphology of their seizures will be studied to identify whether the seizure pattern changes over time or remain the same. In this context, two seizures differing only in amplitude and duration were not considered as a different seizure pattern, as this is considered to be a consequence of a difference in intensity of the electrical activity rather than a different seizure pattern.

4.2.2 Hypothesis testing: There is a significant relation between location of seizure onset and location of interictal activity in the whole population

This pre-specified hypothesis is based on the fact that knowing that any insult of a cortical region within the frontal lobes may lead to a frontal lobe epileptic focus, it is logic to think that the expression of both the interictal and ictal epileptiform waves arise from that lessoned region. Analogically, their maximal expression in the surface EEG is expected to be located in the same electrode.

To test this hypothesis, the subgroup of patients with at least one registered seizure will be selected. For patients with more than one recorded seizures it is needed that the location of their onset remains unchanged. Provided that the previous hypothesis is confirmed, those patients with more than one registered seizure contributed with the clearest EEG registered seizure. Otherwise this hypothesis can´t be studied, as a clear location of onset is needed.

In order to assess the onset location, the selection of the clearest seizure from an electroencephalographic point of view will be based on the least artefact (ocular, EMG…) and the most clear epileptiform morphology of the ictal recording.

For each patient, one data point for the dominating ictal focus and up to two interictal foci will be used for studying the relation between the location of the interictal foci and onset ictal focus.

This location concordance will be tested at two levels:

- The concordance of individual electrodes
- The concordance of hemisphere

4.2.3 Analysis of a potential relation between location of seizure onset and the morphological aspect of seizure onset

Provided that the first hypothesis is confirmed, a potential relation between the EEG characteristics at seizure onset regarding the location of the interictal focus at its onset will be investigated with a descriptive study.

To analyse this matter, the subgroup of patients with at least one registered seizure will be selected. Those patients with more than one registered seizure contributed with the clearest EEG registered seizure, the selection of the clearest seizure will be performed as previously defined.

The new proposed classification attending the morphology at seizure onset will be used to describe the characteristics at seizure onset, and the location of seizure onset will be described at the following three different levels:

- Individual electrodes

-Electrodes of homologue regions in both hemispheres (Fp1&Fp2; F3&F4; F7&F8)

-Brain hemisphere (left; right)

4.2.4 Analysis of the frequencies during seizures

a) Description of the progressive slowing of the frequencies after the ictal onset

Many authors have described the progressive slowing of frequencies after the ictal onset during a seizure. Therefore the sample will be used for describing this well-known and characteristic phenomenon related to the EEG characteristics of epileptic seizures.

b) Analysis of the frequency at seizure onset

The synchronized rhythm of a seizure can be at any frequency of the spectrum, but some authors have described beta and delta frequencies at frontal seizure onset. The data of the sample will be used to study the frequencies at seizure onset in all the patients with at least one recorded seizure.

4.2.5 Analysis of a potential relation between pathologic antecedents and focus location

Based on the location of the artery trees in the brain, as well as the potential more exposed regions to traumatisms, there might be a relation between the pathological antecedent of the case and the location of the focus.

To investigate whether the data gives evidence for such a relation, the focus location will be analysed depending on the presence of different pathologic antecedents.

4.2.6 Analysis of a potential relation between the morphology of the interictal activity and pathologic antecedent

Based on the fact that many different types of lesions affect the cortical neurons, there might be a relation between the pathological antecedent of the case and the morphological expression of this damage in the way of the interictal epileptiform activity, regarding the three axes classification that will be used to describe the interictal epileptiform frontal activity in the sample.

METHODOLOGY

5. METHODOLOGY

5.1 CHARACTERISTICS OF THE STUDY AND DATA SOURCE

This is a descriptive observational study of electroencephalography in frontal lobe epilepsy.

Data were obtained from the adult electroencephalography section of the Clinical Neurophysiology department at the Vall d'Hebron University Hospital. All available EEG recordings (from late eighties to August 2011) codified as presenting frontal EEG interictal and/or ictal discharges have been reviewed to identify the cases to be included in the study as defined below.

“Case” was defined as patient with frontal region interictal or ictal electroencephalography epileptiform discharges. Frontal regions were considered according with the international system of recording EEG 10/20: Front polar (Fp1, Fp2), Inferior frontal (F7, F8), central-frontal (F3, F4) and mid-line-frontal (Fz). There cases with interictal epileptiform abnormalities also seen in mid temporal regions were only included if the amplitude in temporal regions was clearly smaller than in inferior frontal-anterior temporal regions and/or other frontal regions over the whole EEG recording, understanding these activity as diffusion coming from a frontal focus. Two initially selected cases were excluded due to this reason.

According to this criterion, 175 cases were collected from the electroencephalography section of Clinical Neurophysiology department at the Vall d’Hebron University Hospital. For those cases, all available EEG recordings have been reviewed and considered in the context of this study (A total of at least 461 EEG recordings).

It is important to note that as a digital database for the EEG recordings was implemented in 2008, all selected previous recordings (only available in paper form) are scanned for their inclusion in this study while digital images are available for those

recordings posterior to 2008. Therefore for the newest recordings (after 2008) it was possible to review the same epoch of time with different configurations, by changing electrode settings, amplitude sensitivity, time per page, etc.; whereas the settings for the paper EEG recordings were obviously previously fixed. Furthermore the digital database has facilitated the archiving of the EEG recordings, which explains the higher availability and the more frequent presence of recent studies respect older ones in this study. Old recordings were selected based on a careful review of a pool of EEG recordings with frontal epileptiform interictal or ictal discharges that had been previously classified by Dra. Rosa Rovira due to its EEG morphology of the ictal or interictal discharges, clinical evolution or other electroencephalographic aspects as the register of seizures, or diagnostic pitfalls that were eventually solved.

The study includes recordings dated both prior and later than the initiation of the study, so it is both retrospective and prospective.

5.2 EEG METHODOLOGICAL ASPECTS REGARDING THE GRAPHICAL DESCRIPTION OF THE SAMPLE FOR THE PRIMARY OBJECTIVE

As it has been previously explained, the primary objective of this study is to provide a morphologic description of the frontal lobe interictal and ictal epileptiform activity. For this purpose we will first focus on the interictal analyses and after that, we will describe the ictal activity.

5.2.1 Interictal activity

To perform a detailed and in-depth analyses of the interictal activity it was necessary to consider what aspects define it and could be determinant to differentiate the interictal epileptiform activity while, at the same time enclose all the possible variants showed in the sample. First of all a description of the location of the interictal activity

will be done, showing the distribution of the same regarding single electrodes, homologue regions and hemisphere distribution of the interictal activity. Afterwards the morphology of the interictal activity will be carefully described. For this purpose a three axes classification was used, regarding the morphological aspects considered determinant and representative of the interictal epileptiform activity:

a) The specific waveform

b) Its voltage

c) The EEG activity that follows the waveform.

Taking into account these three morphological parameters, a total of 76 categories result, as it is shown in the table below:

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ RETURNING TO THE BASE-LINE	+ IRREGULAR WAVE
SPIKE	<50µv	1	5	9	13
	50-100µV	2	6	10	14
	100-200µV	3	7	11	15
	>200µV	4	8	12	16
SHARP WAVE	<50µv	17	21	25	29
	50-100µV	18	22	26	30
	100-200µV	19	23	27	31
	>200µV	20	24	28	32
DIPHASIC SHARP WAVE	<50µv	33	37	41	45
	50-100µV	34	38	42	46
	100-200µV	35	39	43	47
	>200µV	36	40	44	48
POLY-SPIKES	<50µv	49	53	57	61
	50-100µV	50	54	58	62
	100-200µV	51	55	59	63

	>200µV	52	56	60	64
IRREGULAR WAVE	<50µv	65	69	73	
	50-100µV	66	70	74	
	100-200µV	67	71	75	
	>200µV	68	72	76	

Each case will be carefully analysed to classify the morphology of the interictal EEG abnormalities regarding these parameters. Their interictal activity will be codified with as many data points as necessary for each case, up to five.

Following the table previously showed, the results, showing the data of each waveform category will be described.

After the description of each of the waveform categories, an overall distribution by morphology is showed, regarding the three axes classification previously explained.

5.2.2 Ictal activity

In a second term, the ictal activity will be described:

First of all the distribution of the seizure onset location in the sample will be shown as well as the frequencies observed at seizure onset. Following to this description, the frequency behaviour after the onset will be studied.

Afterwards, the morphology at seizure onset will be described. To perform a detailed and in-depth morphological analyses of the seizure onset activity it was necessary to consider what aspects were common among several seizures which could be interesting for grouping the seizures regarding them.

Once done these analyses, a new morphological classification for frontal seizures is proposed regarding the electroencephalographic characteristics.

5.2.3 Both interictal and ictal activity

Having described the interictal and ictal data, a graphical description of some of the daily questions will be done to show interesting aspects of both the interictal and ictal activity of some interesting cases.

In this description some remarkable details will be presented. In connection to this matter, different electrodes settings will be described to understand the EEG recordings, and facilitate the identification of seizures and its location whenever possible in cases of high diffusion of the interictal activity. Examples of EEG recordings showing the diffusion of the frontal interictal foci activity to other regions of the cortex with and without seizures will be presented.

5.3 SECONDARY OBJECTIVES. STATISTICAL VARIABLES AND METHODOLOGY

The secondary objectives are constituted by the study of the possible association between different variables of interest, as well as the testing of some of pre-specified hypotheses.

First of all a description of all the variables used in the sample is provided and afterwards a detailed explanation of the statistical methodology used for each of the secondary objectives will be provided.

5.3.1 Description of the variables

For a comprehensive description of the variables, they have been divided into two main groups:

a) Demographics and basic clinical variables:
    - "Sex": binomial variable (woman /man)

- "Year of birth": Used to calculate the current age of the patients that constitute the sample at the time of the study. Data were obtained from the clinical file.
- "Age at seizure onset": Age, in years, at the time of first epileptic seizure. This variable was obtained from the neurology clinical history.
- "Pathologic antecedent": categorical variable codified in the following categories regarding the pathologic antecedent in the clinical file: traumatic, vascular, tumoral, infectious, other (existing but different from the previous, i.e. cortex malformations...), without remarkable antecedents (when none of the data seem of interest to the study)

b) EEG variables

Regarding EEG data the following variables were collected:

- "Recorded seizure": binomial variable for each case (yes/no).
- "Variability of seizure pattern": binomial variable (yes/no; NA for patients with less than two seizures). This variable becomes useful for those patients having more than one registered seizure; for each patients all registered seizures were studied and then it was assessed whether the EEG morphology of the seizure pattern remain similar over time for each patient. The morphology at seizure onset according to the classification proposed and the location of seizure onset must remain the same to be codified as a "similar pattern". Here there will be admitted changes in amplitude and in duration of seizures, interpreting them as differences in intensity of seizures, like part of a continuum...
- "Hemispheric location of focus": categorical variable (left/right/both). This variable codifies the location of the interictal EEG focus activity regarding the hemisphere where is recorded.
- "Localization of interictal activity": categorical variable containing electrode positioning codified regarding the 10/20 international classification, specifically for both frontal lobe electrodes: prefrontal

(Fp1, Fp2), mid-frontal (F3, F4, Fz), inferior-frontal (F7, F8). All the available EEG recordings were reviewed, and for each patients this variable was codified as one-point data or two at most, assessing one most active electrode, or two if there exist the situation where two clearly independent foci appeared in different electrode positions, being impossible to define only one focus regarding the basis of EEG interpretation[11].

- "Morphology of interictal activity": Categorical variable containing the morphology of the interictal activity for a know focus, result of the three axes classification previously explained and showed in the table below:

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ RETURNING TO THE BASE-LINE	+ IRREGULAR WAVE
SPIKE	<50µv	1	5	9	13
	50-100µV	2	6	10	14
	100-200µV	3	7	11	15
	>200µV	4	8	12	16
SHARP WAVE	<50µv	17	21	25	29
	50-100µV	18	22	26	30
	100-200µV	19	23	27	31
	>200µV	20	24	27	32
DIPHASIC SHARP WAVE	<50µv	33	37	41	45
	50-100µV	34	38	42	46
	100-200µV	35	39	43	47
	>200µV	36	40	44	48
POLY-SPIKES	<50µv	49	53	57	61
	50-100µV	50	54	58	62

[11] Further information in point 4.2 EEG aspects of the graphical description of the sample

	100-200µV	51	55	59	63
	>200µV	52	56	60	64
IRREGULAR WAVE	<50µv	65	69	73	
	50-100µV	66	70	74	
	100-200µV	67	71	75	
	>200µV	68	72	76	

For each case there have been registered up to five different values when needed, in the case that the morphology of the interictal activity is not a constant but acquire different shapes.

- "Localization of seizure onset": In those patients with seizures, the location of seizure onset was assessed as a categorical variable containing electrode positioning codified by a number for each frontal region electrodes following the same methodology described in the previous variable (Fp1, Fp2, F3, F3, F7, F8, Fz), identifying one of them as the responsible for the seizure onset when possible. The seizures in which it was not possible to identify a scalp EEG seizure origin in a concrete electrode, but a hemisphere predominance was present, the hemisphere was assessed (right / left), as well as was codified as "not localization" when the EEG morphology at seizure onset was not clear enough to asses an individual electrode nor the hemisphere.
- "Characteristics at seizure onset": Categorical variable for different EEG morphology at seizure onset. For each case with recorded seizure and given the fact that the morphological pattern at seizure onset remains unchanged over time for each patient, one EEG seizure recording was selected to codify its morphology. When two or more EEG recordings with seizures were available we selected the one with least artefact and best visual EEG to study this variable. EEG morphology at seizure onset was studied, regarding the frequencies at onset, its amplitude and the waveforms a morphological classification is proposed and used. This

classification differentiate four possible pre-specified EEG onset morphological possibilities: “Synchronized rhythm without a prominent change in amplitude”, when the normal oscillations of activity were lost at seizure onset and a fixed rhythm were in one concrete electrode instead; “Low amplitude and fixed synchronized rhythm” when the attenuation of amplitude was prominent but you can still see the fast frequencies of the RR at onset; “attenuation” when the most remarkable characteristic is the attenuation of the amplitude just before/at the seizure onset, being not possible the assessment of a certain frequency at seizure onset; “Sharp wave/spikes superimposed in a slow wave”, when there were some sharp waves/spikes superimposed in a delta slow wave as the EEG morphological characteristic at seizure onset, followed by the developed seizure with the synchronized rhythm.

- “EEG frequency of seizure”: Regarding the frequencies that constitute the seizure (having selected one seizure by case when available) as previously described The first three frequencies after seizure onset were assessed with its durations in six variables, one referred to the frequency and other to the duration of the specific frequency: Morp1Frec, Morp1Dur, Morp2Frec, Morp2Dur, Morp3Frec, Morp3Dur.

5.3.2 Statistical methodology used for each of the secondary objectives.

Having described the variables studied, the methodology for the analyses of the secondary objectives is presented:

1-Hypothesis testing: Location and morphology of seizure pattern remains the same over time for each patient.

To test this hypothesis, the subgroup of patients with at least two registered seizures will be selected. For those patients, the location at onset and morphology of their

seizures will be studied to identify whether the seizure pattern changes over time or remain the same. In this context, two seizures differing only in amplitude and duration were not considered as a different seizure pattern, as this is considered to be a consequence of a difference in intensity of the electrical activity rather than a different seizure pattern, as previously explained.

The statistical study is the distribution of the categorical variable previously described "variability of seizure pattern" in the sample. The test used for testing the hypothesis is related to the proportion (theta) on a binomial distribution, expected to be of 0,5 at random (H0).

2-Hypothesis testing: There is a significant relation between location of seizure onset and location of interictal activity in the whole population.

To test this hypothesis, the subgroup of patients with at least one registered seizure will be selected. For patients with more than one recorded seizures it is needed that the location of their onset remains unchanged. Provided that the previous hypothesis is confirmed, those patients with more than one registered seizure contributed with the clearest EEG registered seizure. Otherwise this hypothesis can´t be studied, as a clear location of onset is needed.

The variables studied in this case are the "location of seizure onset" and the "location of the interictal activity"

In order to assess the onset location, the selection of the clearest seizure from an electroencephalographic point of view will be based on the least artefact (ocular, EMG…) and the most clear epileptiform morphology of the ictal recording.

For each patient, one data point for the dominating ictal focus and up to two interictal foci will be used for studying the relation between the location of the interictal foci and onset ictal focus.

This location concordance will be tested at two levels:

- The concordance of individual electrodes

- The concordance of hemisphere

For this hypothesis a Chi –square test is perform, and the lambda coefficient used for measuring the degree of association on a scale of 0 to 1.

3-Analysis of a potential relation between location of seizure onset and the morphological aspect of seizure onset

Provided that the first hypothesis is confirmed, a potential relation between the EEG characteristics at seizure onset regarding the location of the interictal focus at its onset will be investigated with a descriptive study.

To analyse this matter, the subgroup of patients with at least one registered seizure will be selected. Those patients with more than one registered seizure contributed with the clearest EEG registered seizure, the selection of the clearest seizure will be performed as previously defined.

The new proposed classification attending the morphology at seizure onset will be used to describe the characteristics at seizure onset, codified in the variable "Characteristics at seizure onset" and the location of seizure onset classified in the variable "location of seizure onset" will be described at the following three different levels:

- Individual electrodes

-Electrodes of homologue regions in both hemispheres (Fp1&Fp2; F3&F4; F7&F8)

-Brain hemisphere (left; right)

Chi-square test is performed to study the potential relation between variables.

4-Analysis of the frequencies during seizures

The sample will be used for describing the well-known phenomena of progressive slowing of frequency during epileptic seizures as well as to analyse the frequency at seizure onset in all patients with at least one recorded seizure.

For this purpose the variables the previously defined variables regarding the description of frequencies during seizures ("Morp1Frec", "Morp2Frec" and "Morp3Frec") will be described. The mean of each variable is then compared with the other groups, studying with a Chi-square test whether the difference between mean frequencies is significant, once the Kolmogorov-Smirnov confirmed a normal distribution. Chi-square is also used for testing a potential relation between location of seizure onset and frequency at onset.

5-Analysis of a potential relation between pathologic antecedents and focus location

To investigate whether the data gives evidence for such a relation, the focus location codified in the variable "interictal location of focus" will be analysed depending on the presence of different pathologic antecedents classified in the variable previously described. A Chis-square test is performed in first place, and then a multifactorial analysis is used for looking for clusters.

6-Analysis of a potential relation between the morphology of the interictal activity and the pathologic antecedent.

Based on the fact that many different types of lesions affect the cortical neurons, there might be a relation between the pathological antecedent of the case and the morphological expression of this damage in the way of the interictal epileptiform activity, regarding the three axes classification that will be used to describe the interictal epileptiform frontal activity in the sample.

For this analysis, the variable of “morphology of the interictal activity” codified as previously described will be studied regarding the pathological antecedent variable with a statistics multifactorial analyses.

RESULTS

6. RESULTS

6.1 DESCRIPTION OF THE SAMPLE: Demographics and basic clinical variables

A total of 175 patients were included in the study. As shown in Table 1, the sample is composed by slightly more men than women (54,9% versus 45,1%) and the mean age of the patients at the moment of closing the sampling (October 2012) is 49 years old (min: 19, max: 97). The age distribution by groups of 10-years is presented.

Total number of patients		175
Gender[1] n (%)	Women	78 (45.1%)
	Men	95 (54.9%)
Age by 2012[1](years)	Mean (SD)	48,9 (18.9)
	Min- Max	19- 97
Age by end 2012 group[1] (years) n (%)	<30	19(10.9%)
	30- 39	45 (25.9%)
	40- 49	42 (24.1 %)
	50- 59	21 (12 .1%)
	60-69	16 (9.2 %)
	70-79	16 (9.2 %)
	80-89	11 (6.3 %)
	≥90	4 (2.3%)

[1] Missing data 2 patients

Table 1. Demographics.

The pathological antecedents were codified in four different groups: "traumatic", "vascular", "tumoral", "infectious", "other", and "none of interest". The most frequent group was "traumatic", followed by "tumoral" and "other".

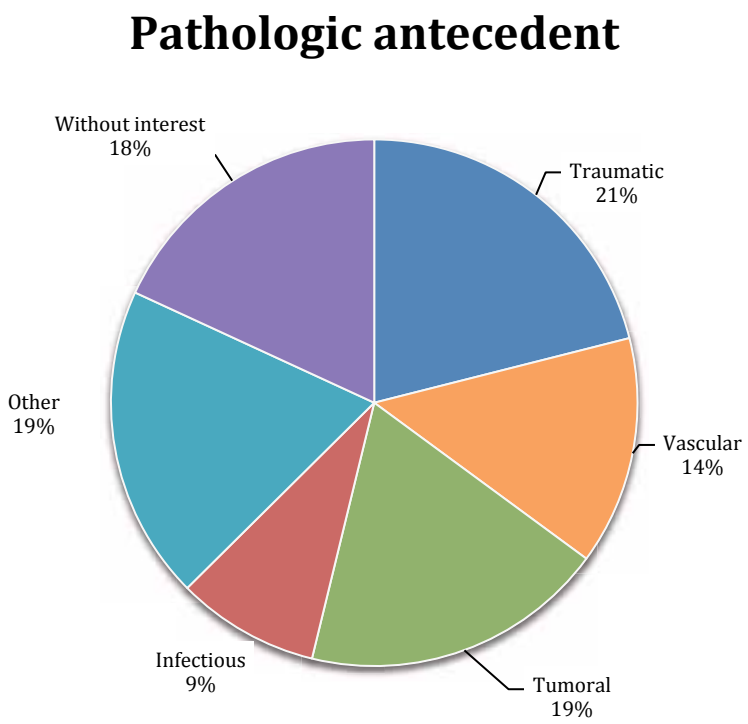


Fig. 5 Pathologic antecedent distribution.

In table 2 is showed its absolute distribution as well as its distribution related to the age of seizure onset.

We can see that the age at seizure onset was of 29,9 years old in the overall sample regardless of the pathologic antecedent.

This ages varies according to the antecedent: We can see a higher mean age of seizure onset in vascular and tumoral cases (42, 9 and 41 years old respectively); the lowest mean age of seizure onset in infectious cases (10, 54 years old) and cases without any pathological antecedent of interest (22, 6 years old),and near to the global mean age for traumatic cases (31 years old). [12]

[12] For detailed information regarding age of seizure onset and pathologic antecedent, look the detailed data in table 2: Age of seizure onset grouped by decades and pathologic antecedent.

		Types of antecedents						
		All types	Traumatic	Vascular	Tumoral	Infectious	Other	Without antecedents of interest and without antecedent at all
Number of patients[1]		175	35 (20%)	23 (13,1%)	32 (18,3%)	14 (8%)	31 (17,7%)	33 (18,9%)
Years at seizure onset	Mean age	29,85	31	42,9	41	10.54	24,3	22.6
Years at seizure onset, n (%)	<10	41 (25.3%)	3 (7,3%)	2 (49%)	6 (14,6%)	10 (24,4%)	11 (26,9%)	9 (22%)
	10-19	37 (21%)	9 (24,3%)	7 (18,9%)	3 (8,1%)	0	6 (16,2%)	12 (32,4%)
	20-29	18 (10.2 %)	9 (50%)	1 (5,6%)	1 (5,6%)	2 (11,2%)	2 (11,2%)	3 (16,6%)
	30-39	22 (12.4 %)	5 (22,7%)	2 (9,1%)	4 (18,2%)	2 (9,1%)	6 (27,3%)	3 (13,6%)
	40-49	14 (6.2 %)	3 (21,4%)	1 (7,1%)	6 (42,9%)	0	3(21,4%)	1 (7,1%)
	50-59	9 (5.6 %)	2 (22,2%)	1 (11,1%)	2 (22,2%)	0	1 (11,1%)	3 (33,3%)
	60-69	12 (7.4 %)	3 (25%)	5 (41,6%)	2 (16,6%)	0	1 (8,3%)	1 (8,3%)
	70-79	10 (6.2%)	1 (10%)	2(20%)	6 (60%)	0	1 (10%)	0
	80-89	5 (2.1%)	0	2 (40%)	2 (40%)	0	0	1 (20%)
	>90	0	0	0	0	0	0	0

[1] Missing data for 7 patients

Table2. Age at seizure onset regarding the pathologic antecedent.

6.2 PRIMARY OBJECTIVE: GRAPHICAL DESCRIPTION OF EEG EPILEPTIFORM ACTIVITY.

First of all we will go through the table showed in "methodology", reviewing the morphology the interictal activity acquires. We will locate this activity by using different features of EEG equipment (settings, sensitivity, and screen speed) and then we will go further in the analysis of the epileptiform activity, reviewing ictal activity with its EEG features.

6.2.1 Interictal epileptiform activity.

The interictal epileptiform activity found in the sample will be described regarding its location and afterwards regarding the morphology it shows in the EEG.

a) Location of interictal activity

The assessment of interictal activity was in first placed divided by hemispheric location in left, right, midline, or more than one focus with left and right distribution. In a further step the "location of interictal activity variable" gives each patient a more accurate description using the most active electrode (Fp1/Fp2/F3/F4/F7/F8/Fz).

The results in the sample are the following:

Left focus	Right focus	Midline focus	both left and right
79	76	4	16

We can see that the mid-line expression of the focal activity is very unusual in the sample, and most of the cases had only one interictal activity with a clear hemispheric dominance.

The distribution shows an almost equal expression for both right and left hemisphere. There are also cases with more than one focus, with a 9 % of cases with both a right and left foci.

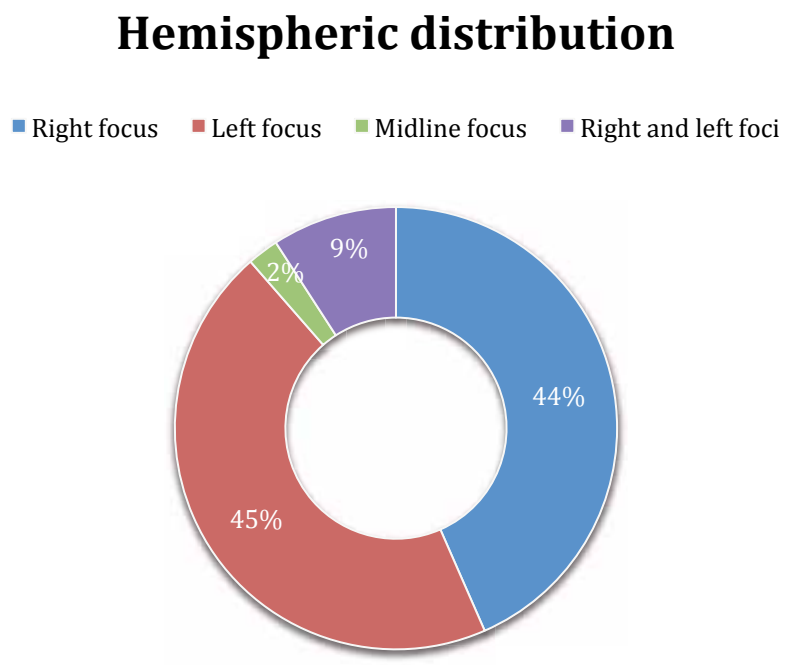


Fig. 6 Hemispheric distribution of interictal activity.

Regarding the most expressive electrode, the specific distribution by location of the interictal activity is as follows:

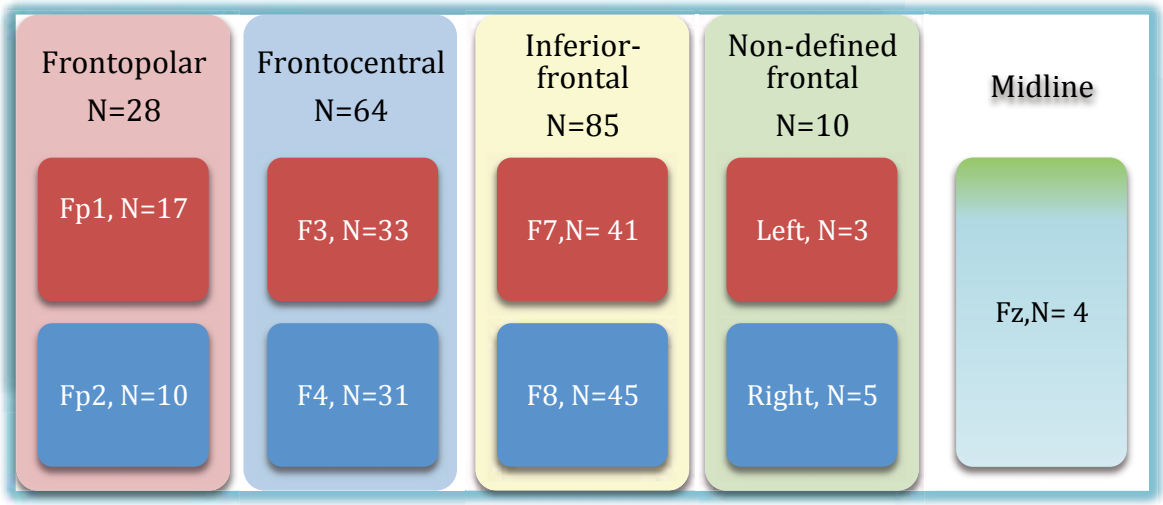


Fig. 7 Distribution of interictal activity in different regions of the frontal lobes.

As we can see in Fig.7 and 8, the most frequent location for the interictal activity in the sample is the inferior-frontal (85 cases) followed by the front central region (64) and, pre-frontal (28). In 10 cases this activity could not be assigned an electrode with certain, being codified as left or right.

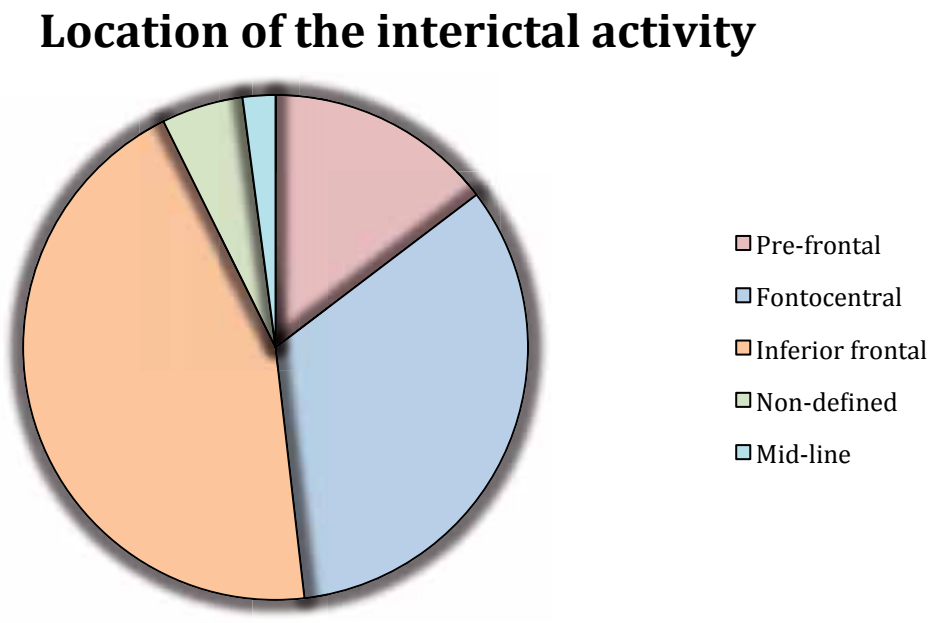


Fig. 8 Regions with maximal expression of the interictal activity.

In Fig 7 we can appreciate that there is no difference between hemispheres for each location of the frontal lobes, and the mid-line maximal expression is very odd in our sample.

Non-defined frontal was codified when the electrode settings of recording didn't include the complete setting of the 10/20 international system of recording and instead, a reduced electrode setting was used. In those cases the lack of some electrodes made it impossible to assess the most active one.

b) Morphology of the interictal activity

We have tried to enclose all the possibilities for the interictal epileptiform activity shapes observed in the sample. With that idea in mind we have carefully observed the

factors that lead to differences in the EEG recordings and we have observed that we needed a classification that would take into account:

- the epileptic waveform itself,
- its voltage,
- the activity that follows the epileptiform wave.

This results in a classification based on these three axes that we have organized into a table that synthesizes the previously specified three different EEG aspects.

This is a novel way to view the interictal epileptiform EEG activity, as no other authors have reported such differentiation. We think that this morphological analysis of the waveforms may be useful to better understand and identify frontal focal epileptiform activity, and it is another important piece of information for the EEG reader.

We think that this high specialized classification is important to deep in the knowledge of the focal expression of the epileptiform activity, and try to study is there are specific characteristics that may be useful in the diagnose of frontal epilepsies or focal epilepsies versus generalized ones.

For characterising the interictal activity regarding the items previously commented as important for us, we have created a table that take into account several items: The morphology of the wave, its amplitude, and the waveform that follows after the epileptiform wave. This results into the previously showed 76 different possibilities that we are going to explain right away.

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ SLOW RETURNING TO THE BASE-LINE	+ IRREGULAR WAVE
SPIKE	<50µv	1	5	9	13
	50-100µV	2	6	10	14
	100-200µV	3	7	11	15
	>200µV	4	8	12	16
SHARP WAVE	<50µv	17	21	25	29
	50-100µV	18	22	26	30
	100-200µV	19	23	27	31
	>200µV	20	24	28	32
DIPHASIC SHARP WAVE	<50µv	33	37	41	45
	50-100µV	34	38	42	46
	100-200µV	35	39	43	47
	>200µV	36	40	44	48
POLY-SPIKES	<50µv	49	53	57	61
	50-100µV	50	54	58	62
	100-200µV	51	55	59	63
	>200µV	52	56	60	64
IRREGULAR WAVE	<50µv	65	69	73	
	50-100µV	66	70	74	
	100-200µV	67	71	75	
	>200µV	68	72	76	

Fig. 9 Classification of interictal epileptiform activity regarding shape, voltage and following activity.

We can easily imagine that one case can have several waveforms within the same EEG recording, or in different EEG recordings. This make that each patient has several data for this morphological analysis[13].

As we can see, there are five different possibilities as "waveforms", four of them specific of epilepsy: Spike, sharp wave, diphasic sharp wave and poly-spikes. We have added "Irregular wave" as another non specific waveform that can be found in these patients added to some of the other categories.

Each EEG recording has been reviewed and the shape was assessed using up to five different shapes of the table per patient.

Now we are going to detail one by one the categories, showing the results that we have obtained using this method regarding the morphological aspects. The distribution of the frontal interictal epileptiform activity is as follows:

- **"Spike"**

Spike is an epileptiform wave of less than 70 ms. of duration. As we can see in the table below we have divided them according to its voltage and the following EEG activity. This is the distribution of the "spike" group in the sample.

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ SLOW RETURNING TO THE BASE-LINE	+ IRREGULAR SLOW WAVE
SPIKE	<50µv	21	1	0	2
	50-100µV	9	3	0	10
	100-200µV	4	2	3	6
	>200µV	2	0	4	1

Fig. 10 Distribution of the spike group in the sample.

[13] For instance patient 8 REL has three data point (6, 20 and 66) this means that he have spikes of 50-100 µV followed by a slow wave, sharp waves of more than 200 µV isolated and some irregular waves of 50-100 µV.

Graphically, regardless the voltage, we can see that the most common way of appearance for the spike is “isolated”, and on a second place, “followed by an irregular slow wave”

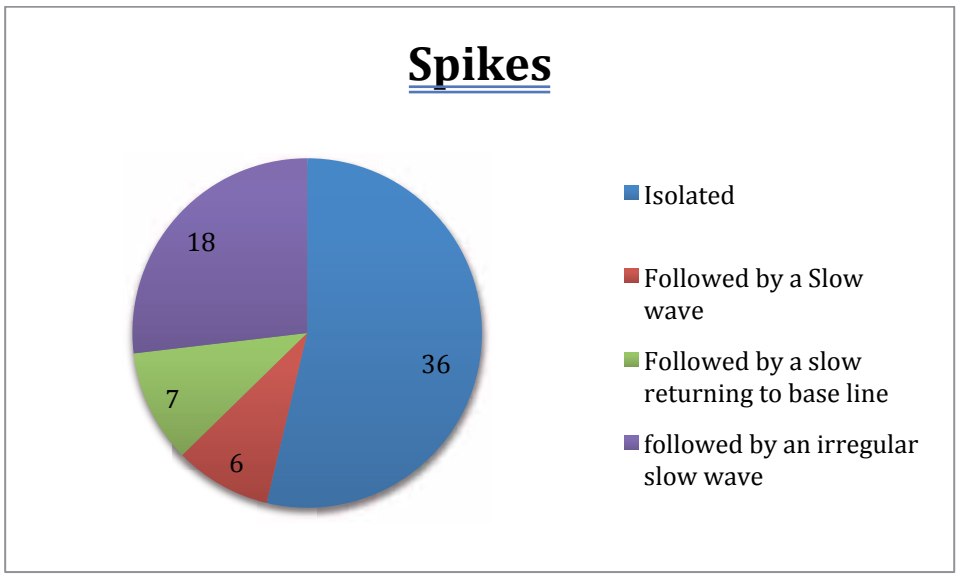


Fig. 11 EEG activity after the spike.

If we want to analyse also the voltage, for isolated spikes most of them had a rather low voltage of less than 50µV, as we can see in Fig. 12.

Amplitude

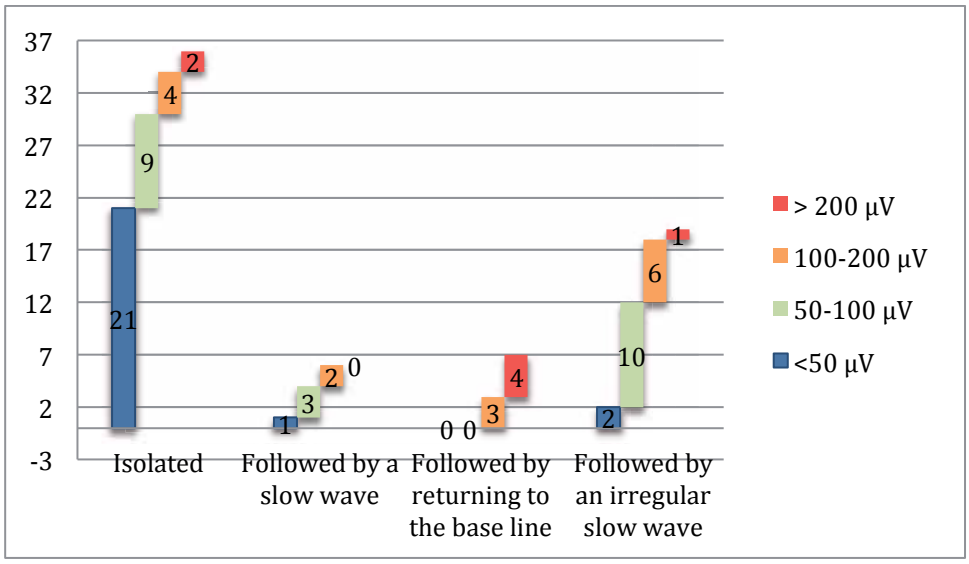


Fig. 12 Graphical description of the spikes, regarding the voltage.

The group that showed spikes as interictal activity has the distribution previously showed. The most numerous group has been by far “isolated spikes” with 35 cases out of 65. The more frequent amplitude in this group (isolated spike) is less than 50μV and 50-100 μV, which constitute 30 cases out of the 35.

The second most common group has been the one constituted by “spike followed by an irregular slow wave”, with 19 cases out of 65. In this group (“spike followed by an irregular slow wave”) the voltage range most commonly seen is 50-100 μV.

Graphical example of the possibilities within this category in the sample:

Isolated spike:

Isolated spike have been the most frequent group within the “spike group”.

36 cases had isolated spikes, being the most common low voltage isolated spikes, of less than 50 μV.

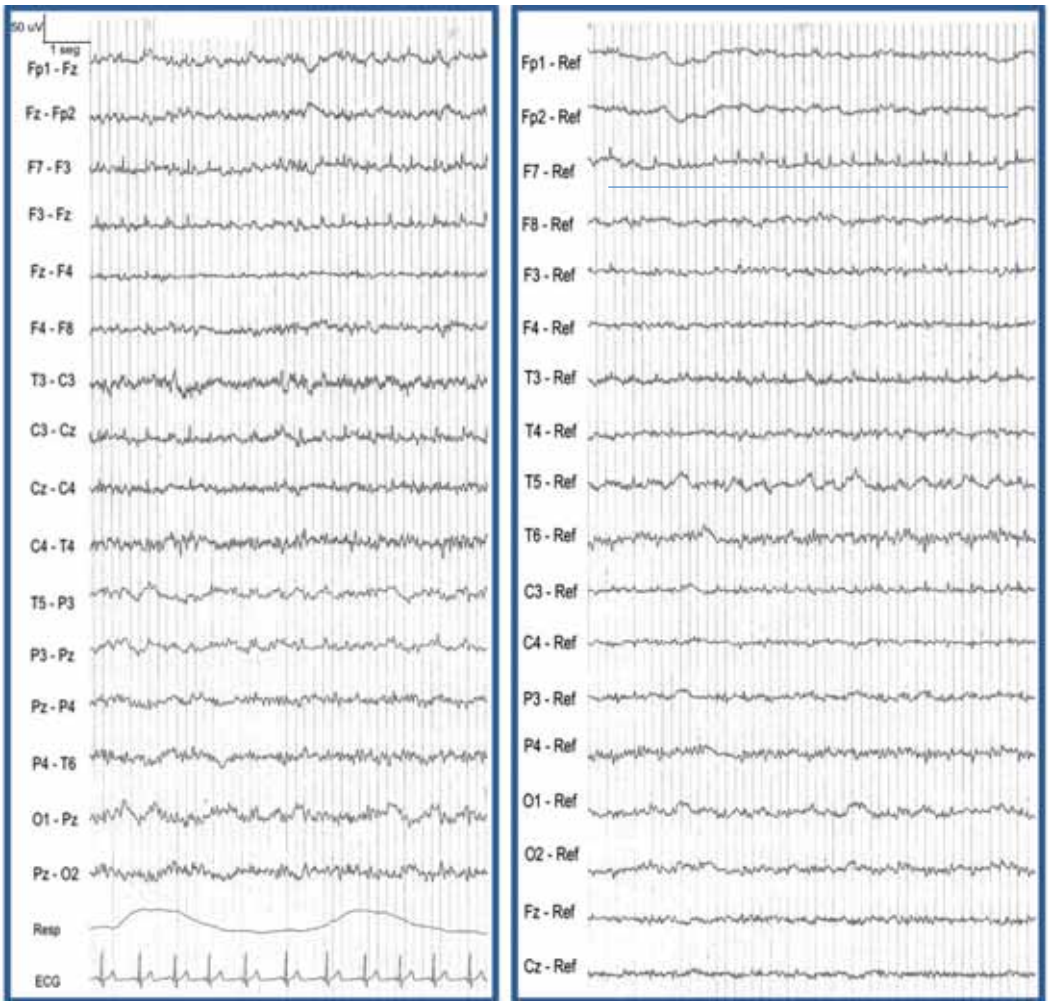


Fig. 13 Case 6. Isolated spike of less than 50 μV with maximal expression in F7>F3. Case commented on the graphical appendix (S.R.S.)

The picture above shows an interictal shape of isolated spikes of less than 50 μ V in left frontal regions. Two electrode settings are shown: Transversal (bipolar) and average one (referential). A good approach for locating the interictal epileptiform activity is to always use more than one electrode settings, to better understand the location and shape of the epileptiform activity. Low voltage spikes can be sometime misleading, and can be both erroneously assessed in a situation where ECG artefact is recorded or on

the contrary it can be missed. The simultaneously recording of ECG activity is essential to avoid this error.

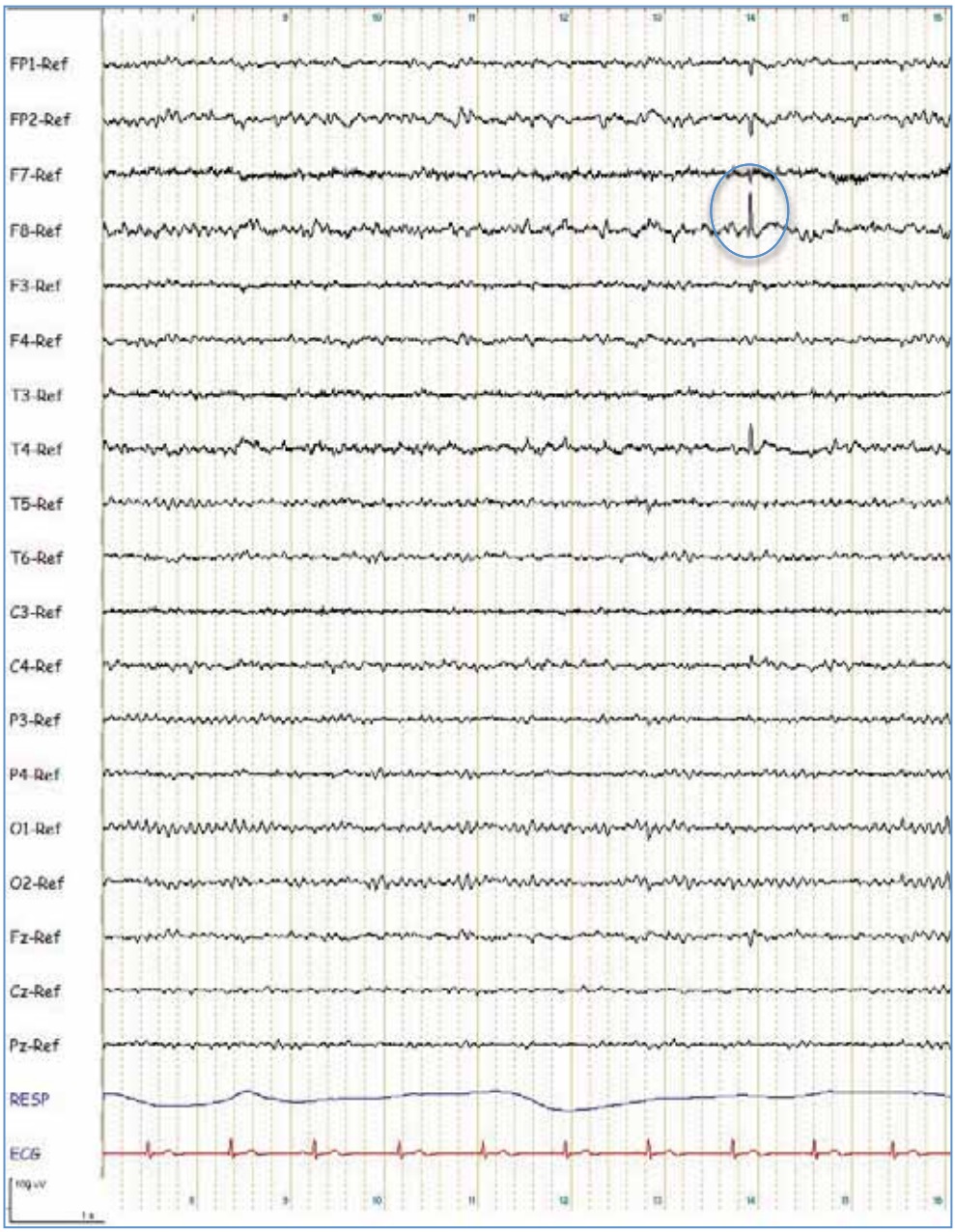


Fig. 14 Case 73. Isolated spike 50-100 μV with maximal expression in F8>T4,C4.

Fig.14 shows another example of spike shape as interictal epileptiform activity, showed by an average electrode setting, with inferior-frontal right electrode (F8) being the most active, and in this case the amplitude is a bit higher. Amplitudes between 50 and 100 μV was the second most common group among isolated spikes.

Spike followed by a slow wave:

There were five cases in which interictal shape was a spike followed by a slow wave.

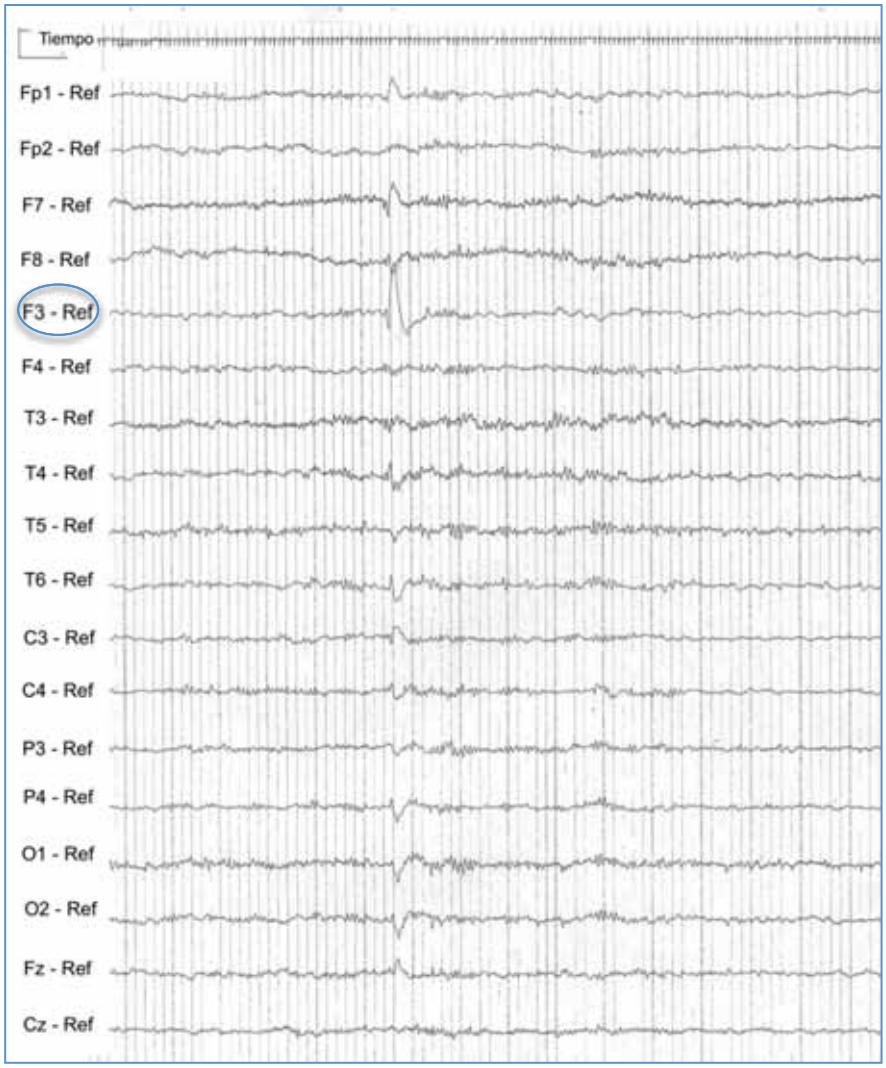


Fig. 15 Case 49. Spike followed by a slow wave with maximal expression in F3

Graphical example of the shape with more detail:

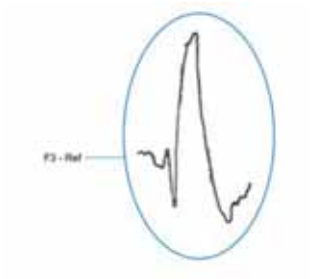


Fig. 16 Detailed view of a spike followed by a slow wave

Sometimes the spike is hardly seen before the slow component of the wave, as in this case. In cases like this one quality to record the EEG is mandatory to obtain a signal as clear as possible.

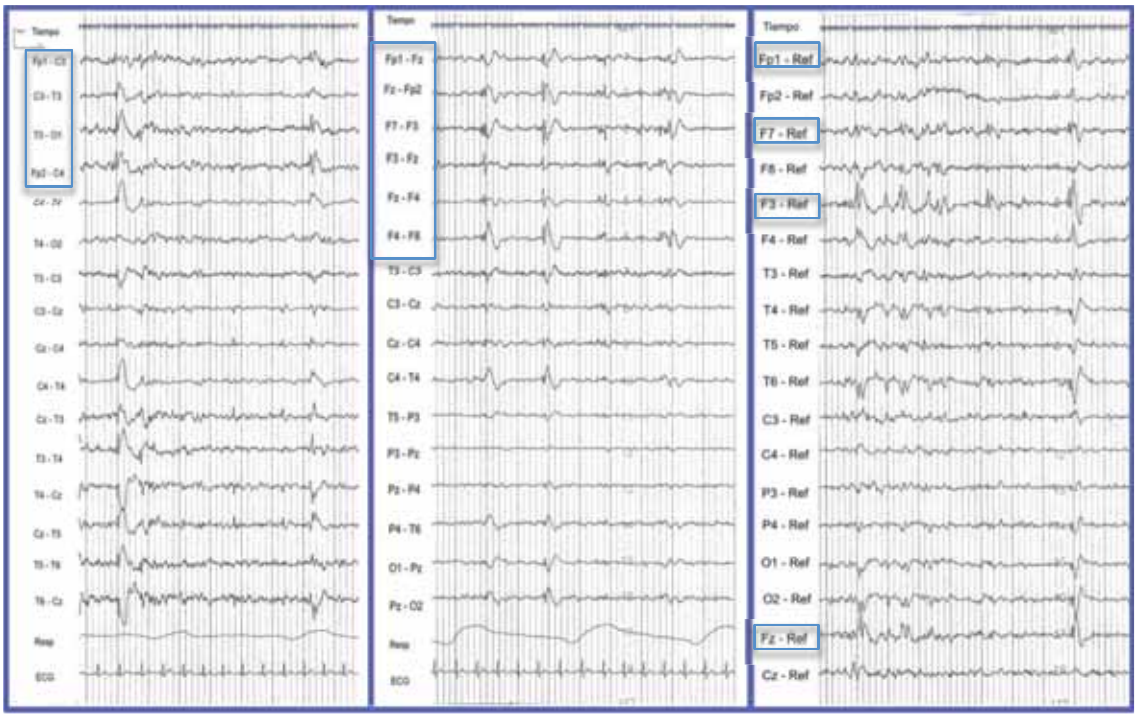


Fig. 17 Case 51. Spike followed by a slow wave with maximal expression in F3>Fz and diffusion to F7, Fp1, F4. Comparative view among different electrode settings: Standard, transversal and referential montages. Case commented on the graphical appendix (J.R.O.)

In Fig.17 we can see another example of a spike followed by a slow wave. This is a very good example to study the aspect that the activity acquires with some of the available electrode settings.

The first and the second are bipolar settings. We can see that in the second one, the "transversal", that the epileptic activity is almost cancelled in "F3-Fz", being precisely this region the most active (F3), as we can confirm in average setting.

Spike followed by the return to the base-line

In some cases, more than a very true slow or an irregular slow wave after the paroxistic shape we can see that in fact, the slow component is the slow returning to the base line.

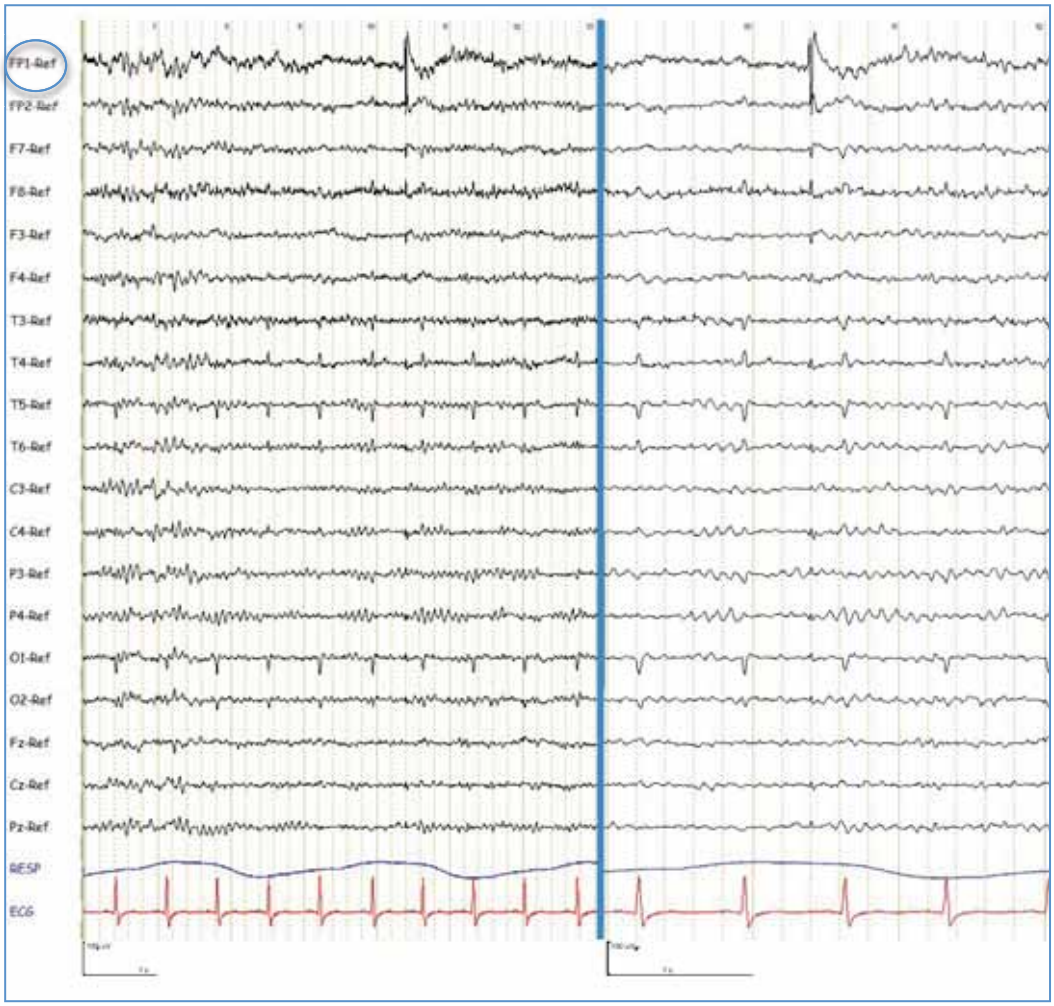


Fig. 18 Case 83.High amplitude spike and the return to the baseline with maximal expression in Fp1. Comparative view between two different speed configurations in a referential montage.

Fig. 18 shows an example of high amplitude and very fast spike. To appreciate better its morphology we show a collage with two time settings. We can see the slow returning to the baseline after the spike in Fig 19 with more detail:

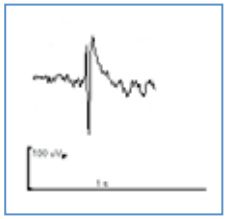
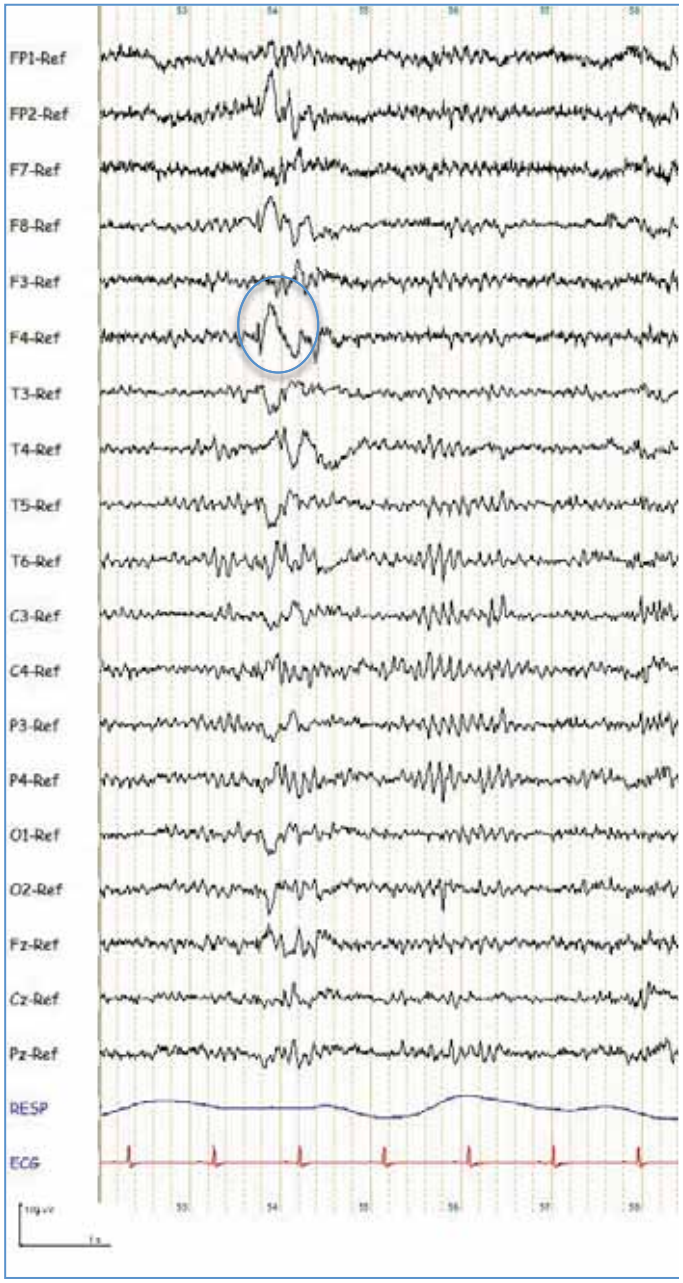


Fig. 19 Detailed view of the high amplitude spike and the return to the base line

Spike followed by an irregular slow wave:



It is fairly common seeing that the spike is followed by an irregular wave. In the sample we found 19 cases with spike followed by an irregular wave as a slow component of the epileptiform interictal activity.

Fig. 20 Case 102. Spike followed by an irregular slow wave with maximal expression in F4 and diffusion especially to Fp2, F8.

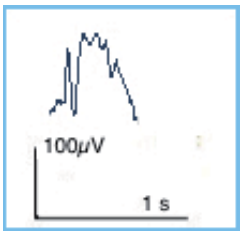


Fig. 21 Detailed view of a spike followed by an irregular slow wave

❖ "Sharp wave"

A sharp wave is an epileptiform wave, sharp in morphology and with duration between 70 and 200ms. As we can see in the table below we have divided them according to its voltage and the following EEG activity.

This is the distribution of the "sharp wave" group in the sample.

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ SLOW RETURNING TO THE BASE-LINE	+ IRREGULAR SLOW WAVE
SHARP WAVE	<50µv	25	0	0	1
	50-100µV	44	5	5	14
	100-200µV	24	2	5	9
	>200µV	1	0	0	1

Fig. 22 Distribution of "Sharp wave" group in the sample.

Graphically, regardless the voltage, we can see that the most common way of appearance for the "sharp wave" is "isolated" by far, and on a second place, "followed by an irregular slow wave"

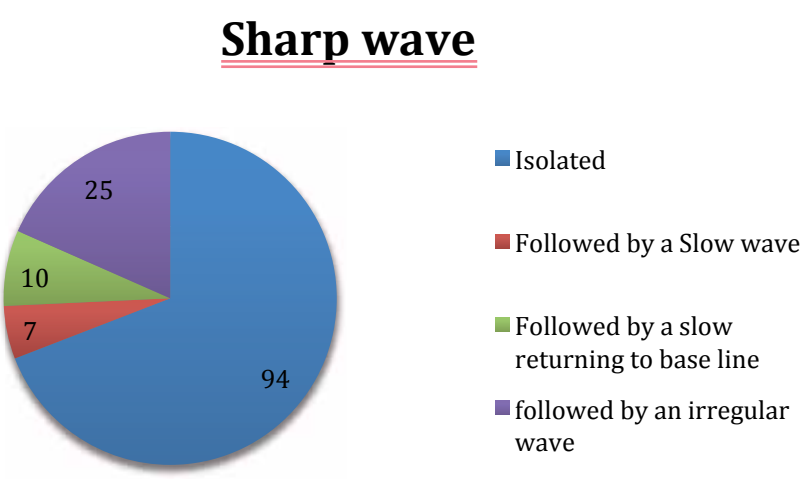


Fig. 23 EEG activity after the "Sharp wave".

If we want to analyse also the voltage we can see the next picture, where we can see a predominance of 50-100 μV in every subgroup of sharp waves.

Amplitude

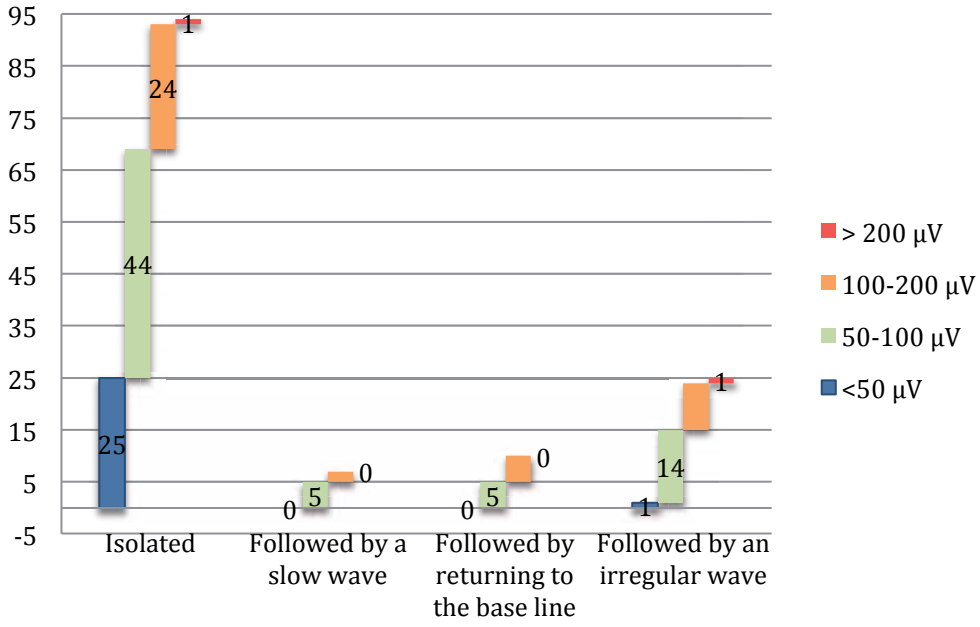


Fig. 24 Graphical description of the sharp wave group, regarding the voltage.

The “sharp wave” has been the most common morphology group found in the sample, as we have already seen in the overall distribution of the sample by morphology. 132 patients out of 176 had sharp waves in their EEG recordings.

The most common sub-group has been the “isolated sharp wave” one with amplitude between 50 and 100 μV, followed by those of less than 50 μV.

Graphical example of the possibilities within this category in the sample:

Isolated sharp wave:

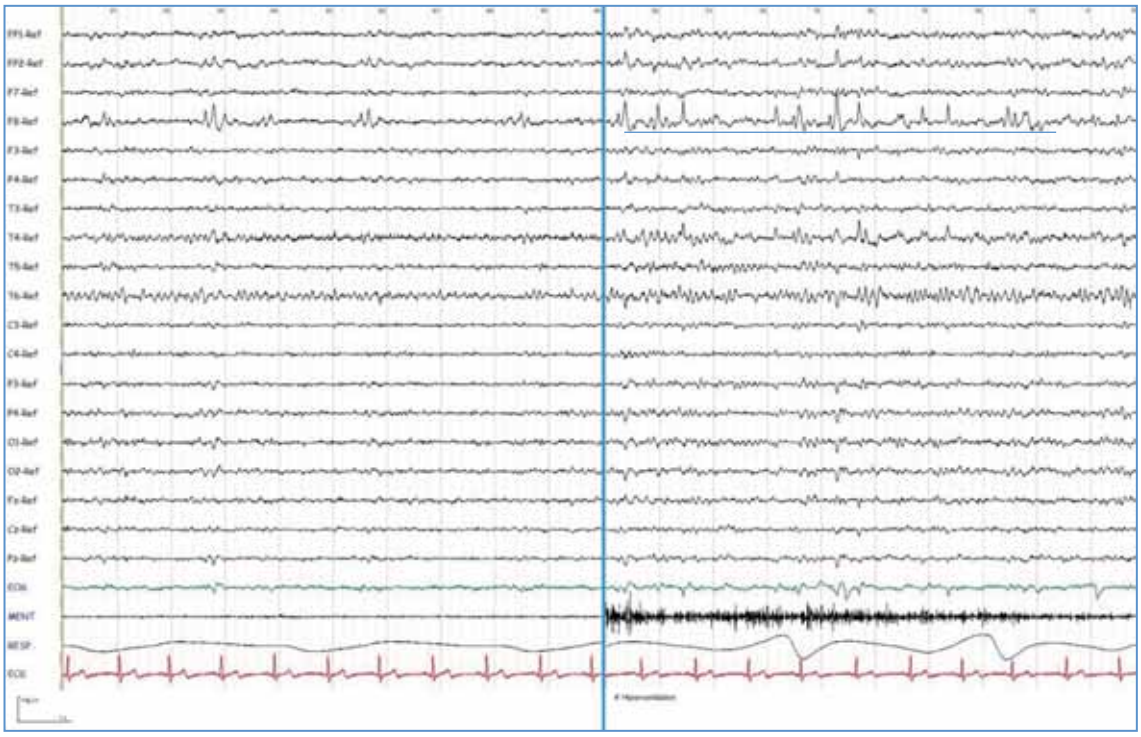


Fig. 25 Case 108.Isolated sharp waves with maximal expression in F8 and diffusion to next temporal region, T4.

In this picture we can see the sharp wave recorded while the patient is normally breathing and also during hyperventilation. There is a remarkable activation and diffusion of the focal epileptiform activity during hyperventilation.

Sharp wave followed by a slow wave

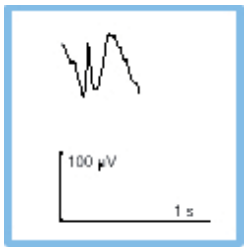


Fig. 26 Detailed view

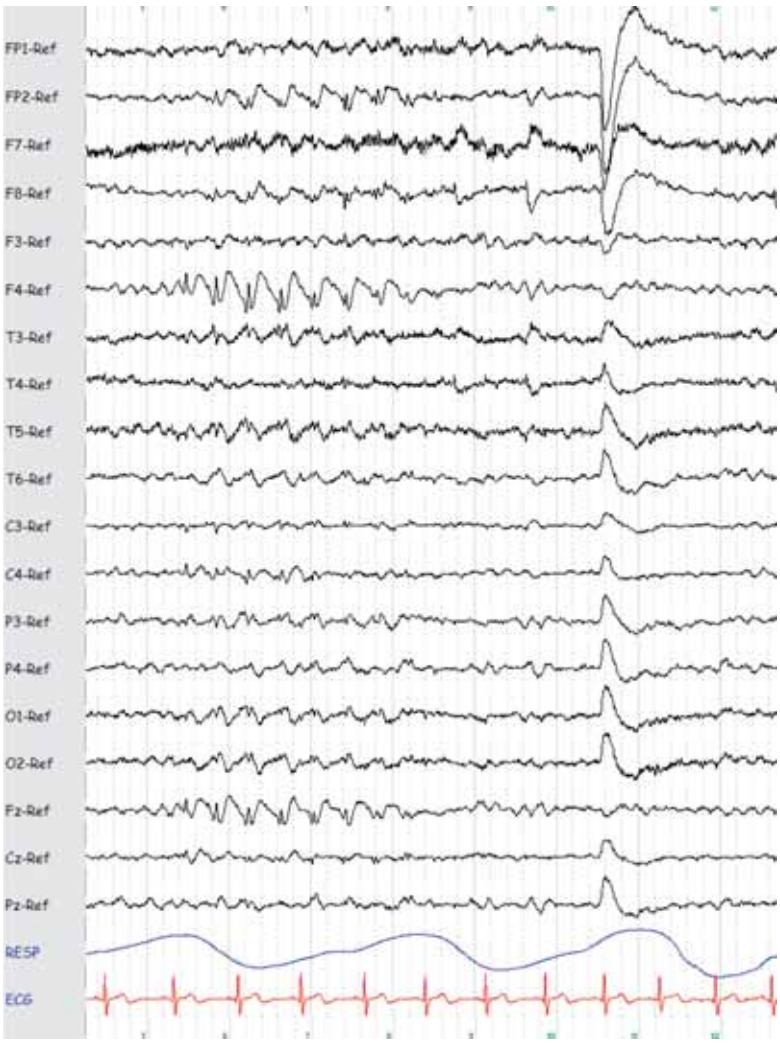


Fig. 27 Case 66. Sharp wave followed by a slow wave with maximal expression in F4 and diffusion to Fz, Fp2.

In this example, with average electrode settings we can see isolated low amplitude spikes in right frontal regions (mainly in F8) as well as sharp waves followed by a slow wave in right front-central region and mid frontal (F4>Fz) with diffusion to other regions.

Sharp wave and its return to the base line

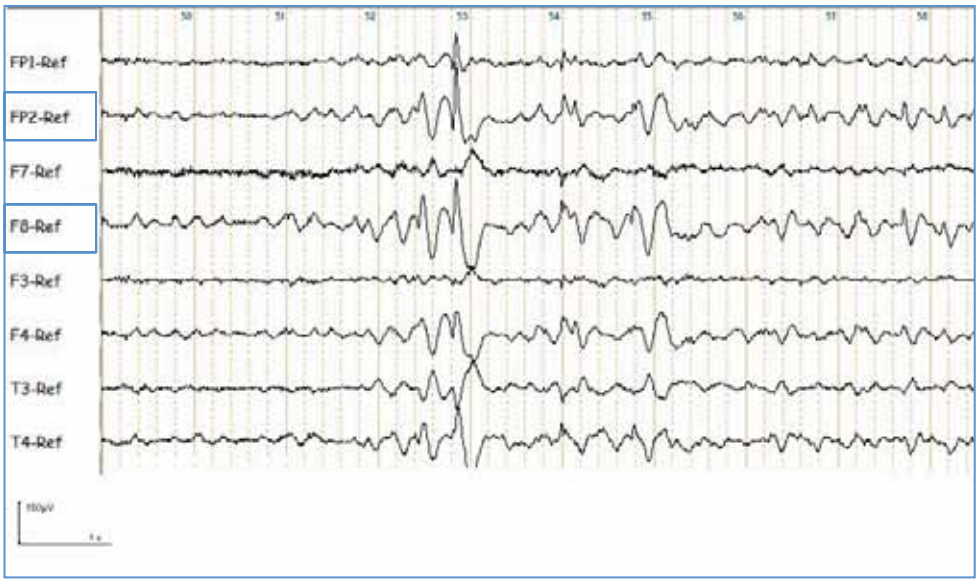


Fig. 28 Case 80. Sharp wave and its following return to the base-line with maximal expression in Fp2 and F8, and diffusion to next regions, F4, T4.

Sharp wave followed by an irregular slow wave

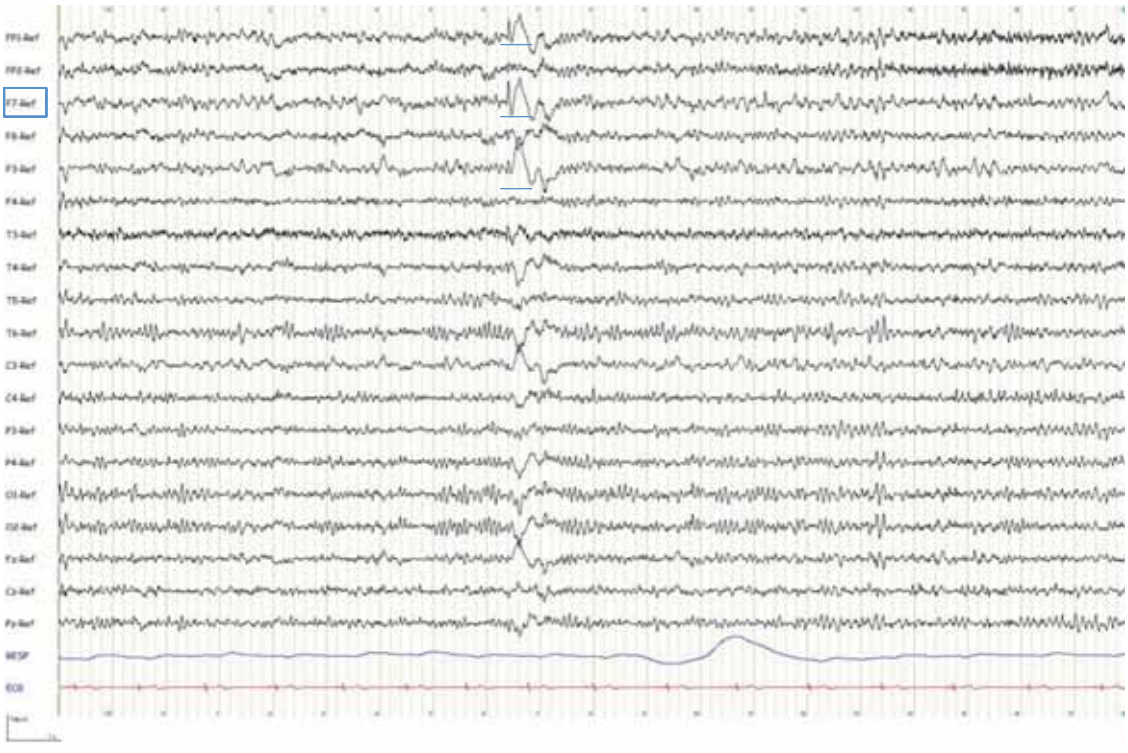


Fig. 29 Sharp wave followed by an irregular slow wave with maximal expression in left inferior frontal region, F7, and diffusion especially to Fp1, F3.

❖ "Diphasic sharp wave"

A diphasic sharp wave is an epileptiform wave, with a sharp morphology and with duration between 70 and 200ms, and two-phases regarding the waveform morphology.

This is the distribution of the "diphasic sharp wave" morphology group in the sample:

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ SLOW RETURNING TO THE BASE-LINE	+ IRREGULAR WAVE
DIPHASIC SHARP WAVE	<50µv	2	0	1	0
	50-100µV	6	1	3	5
	100-200µV	2	4	10	1
	>200µV	0	0	2	0

Fig. 30 Distribution of "diphasic sharp wave" group in the sample.

As we can see in the graphic below, a slow returning to the base line commonly follows the diphasic sharp waves.

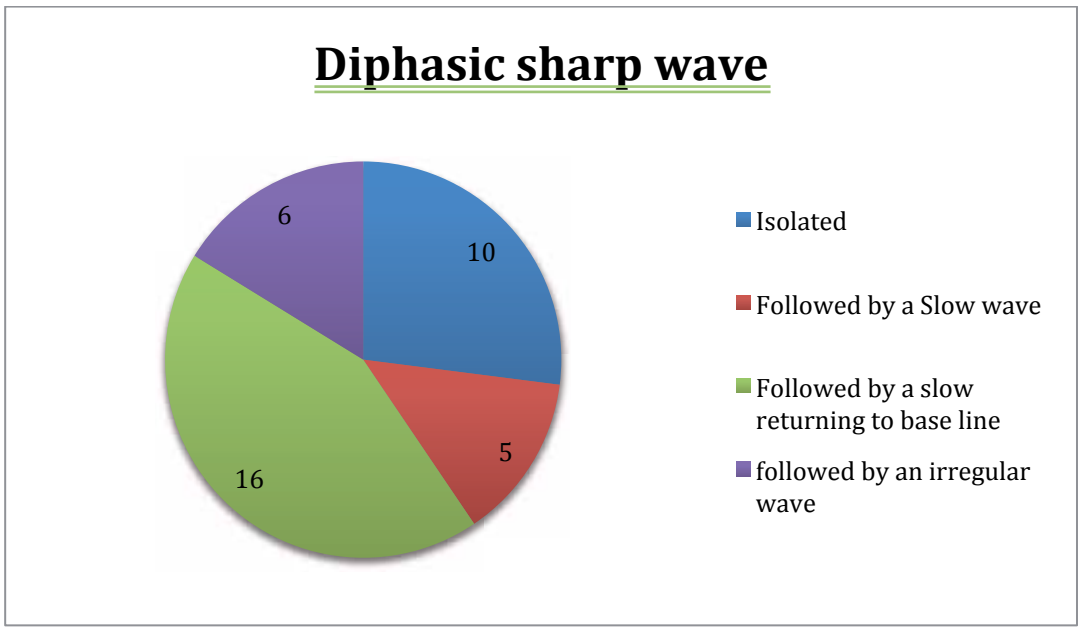


Fig. 31 EEG activity after the diphasic sharp wave.

Regarding the amplitude, they frequently have a voltage between 100 and 200µV, as the graphic below shows.

Amplitude

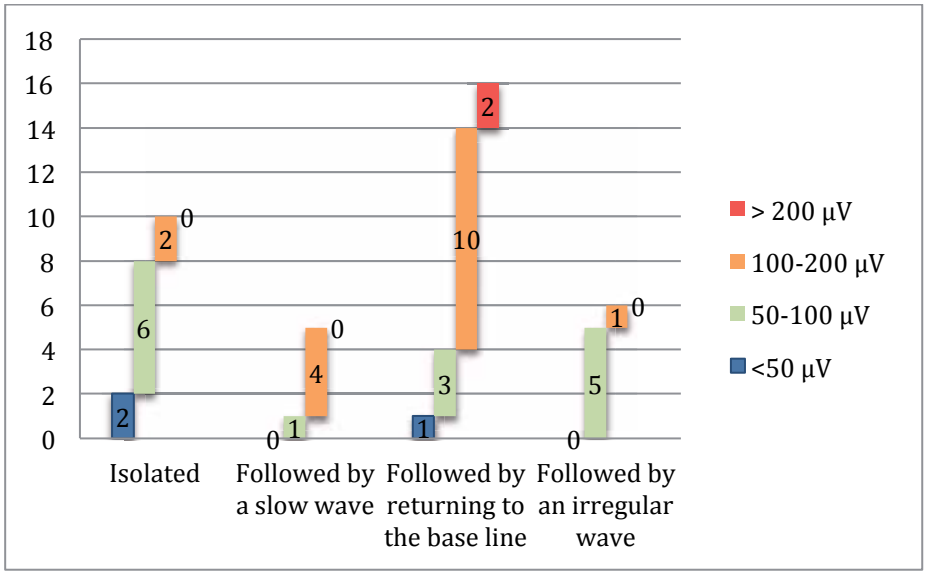


Fig. 32 Graphicaldescription of diphasic sharp wave group, regarding the voltage.

Graphical example of the possibilities within this category in the sample:

Isolated diphasic sharp wave:

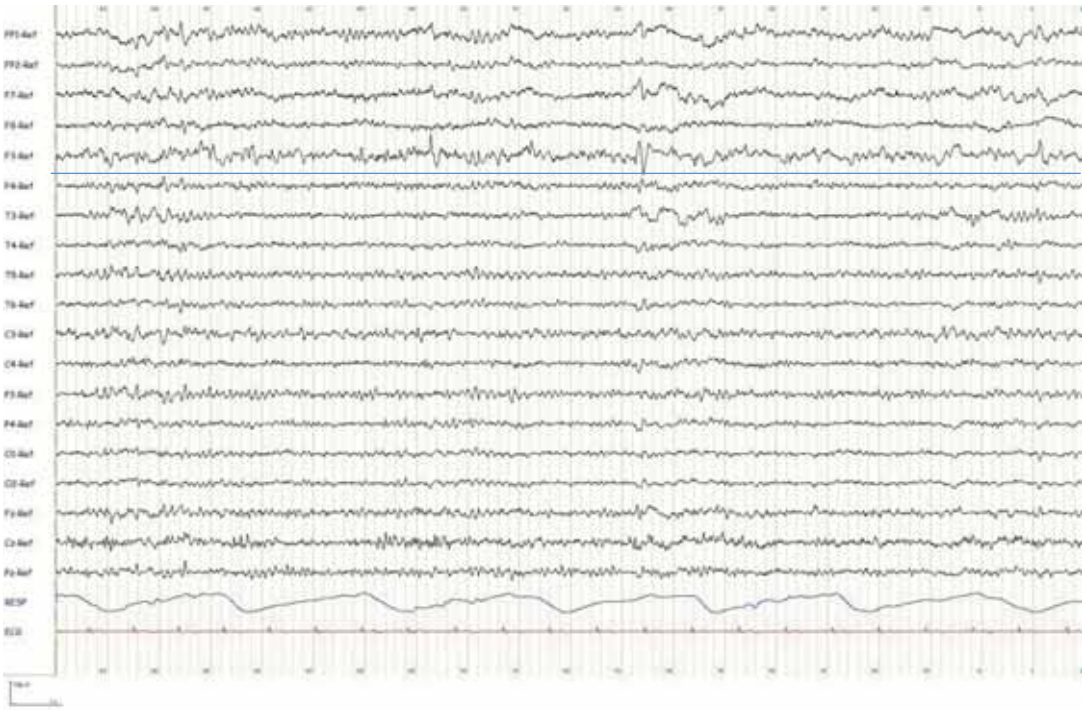


Fig. 33 Isolated diphasic sharp wave with maximal expression in F3.

We can clearly see in this example (Fig.32) that interictal activity tents to have several forms, being able to find irregular theta and delta waves with simple and diphasic sharp waves in left frontal region (F3).

Diphasic sharp wave followed by a slow wave

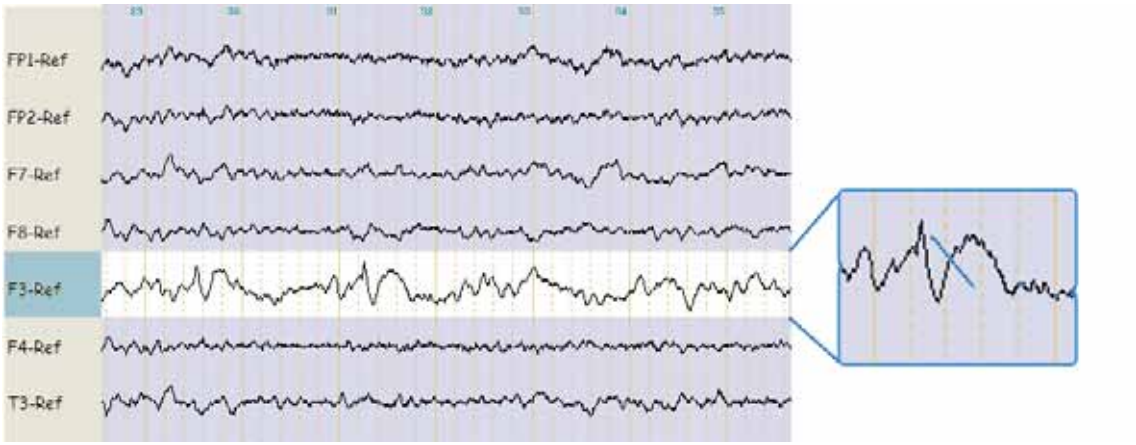


Fig. 34 Diphasic sharp wave followed by a slow wave with maximal expression in F3 region.

This was the only case we were able to find a diphasic sharp wave followed by a slow wave. In the picture, the blue line in the detailed view helps to differentiate the diphasic sharp wave from the slow wave afterwards.

Diphasic sharp wave and its return to the base line

Most of the diphasic sharp waves were followed simple by the return of the electrical activity to the base line.

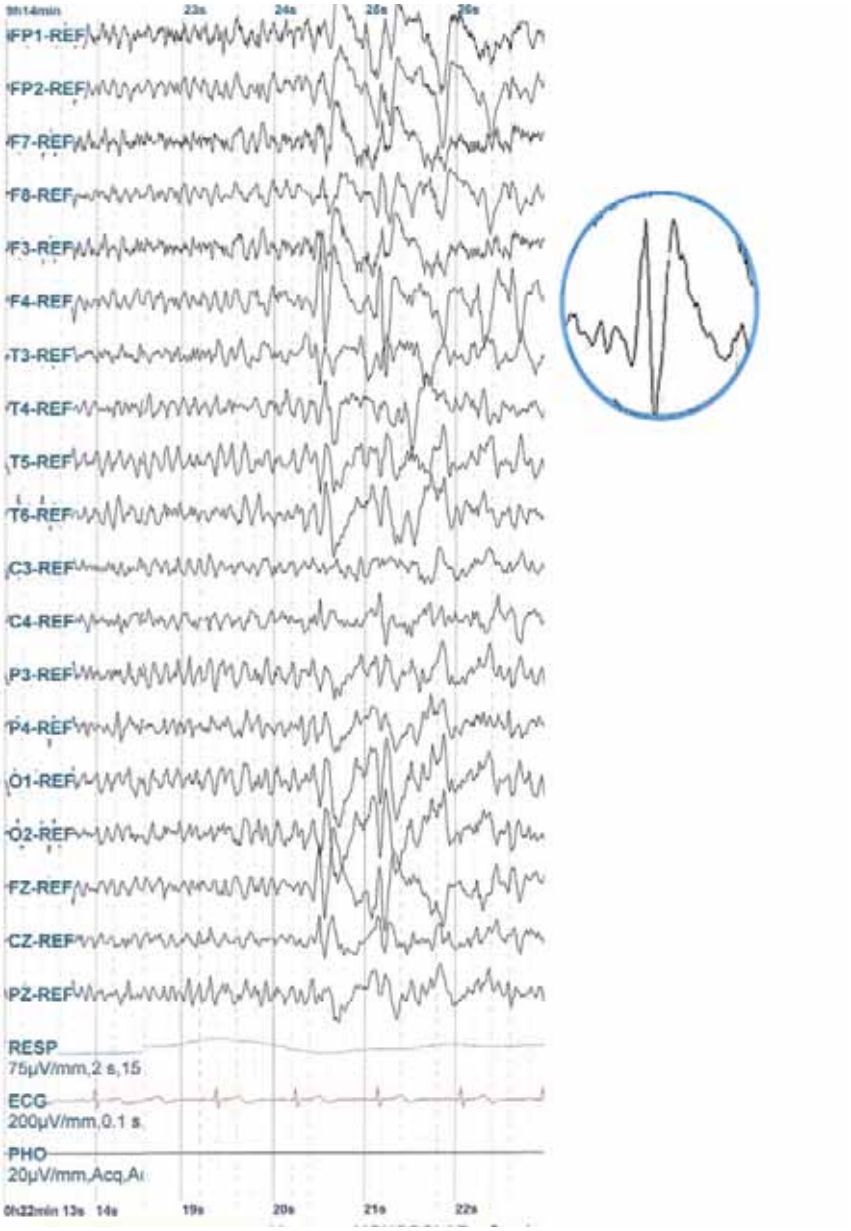


Fig. 35 Diphasic sharp wave and its return to the base-line with maximal expression in right front-central regions, F4>Fz.

We can see that after the diphasic wave, the returning contains activity; it is not a straight line but a wavy line, which differentiate this category.

Diphasic sharp wave followed by an irregular slow wave

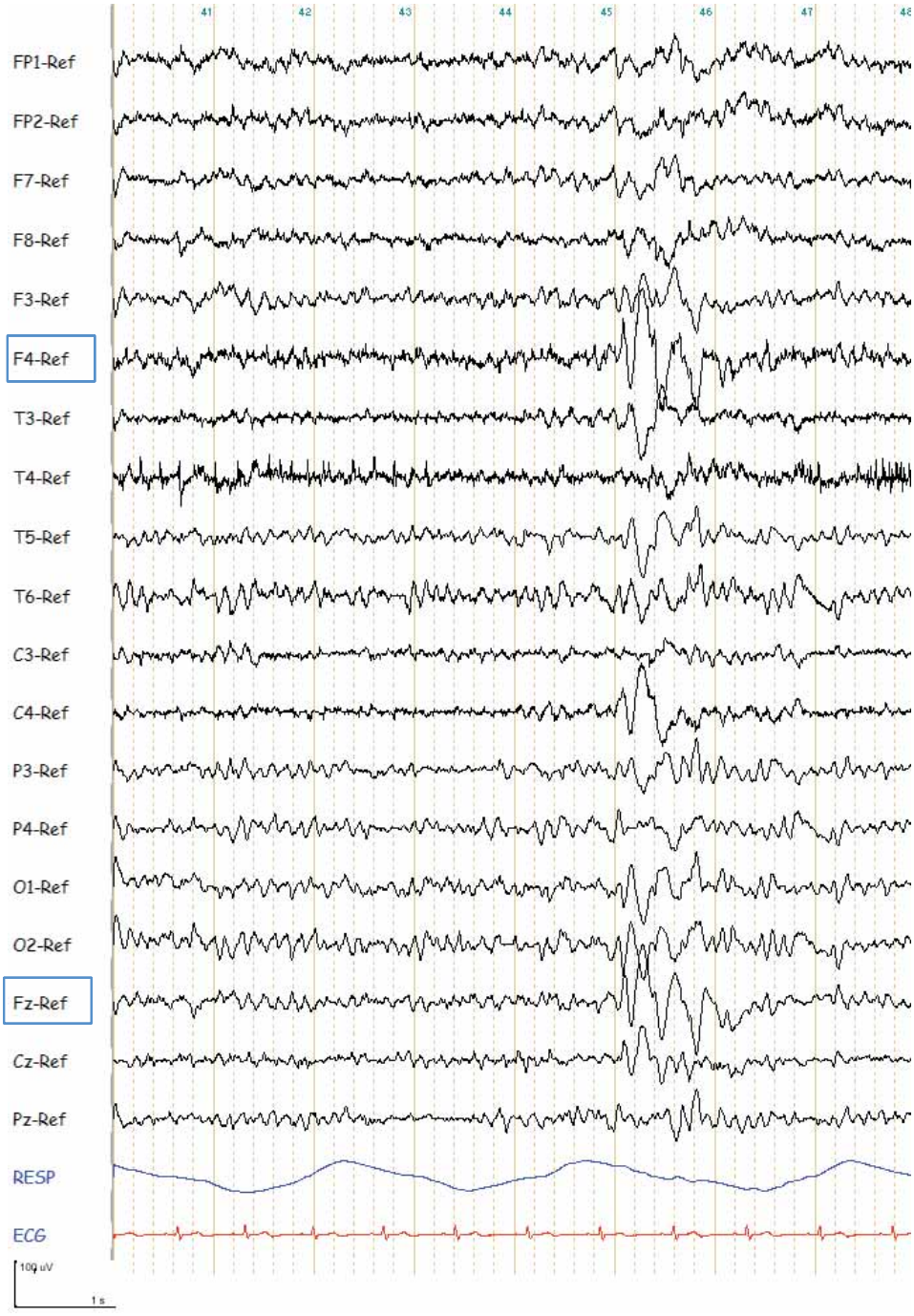


Fig. 36 Diphasic Sharp wave followed by some irregular slow waves with maximal expression in F4, and diffusion to mid-line and central regions Fz, C4.

In right central fontal region and mid-line frontal electrode we can see an epileptiform paroxysm formed by a diphasic sharp wave followed by irregular slow waves.

- **"Poly-spikes"**: A group of three or more spikes as an epileptic morphology of the interictal waves.

As we can see in the table and the graphic below, a few cases showed poly-spikes as epileptic waveform, and almost all were isolated.

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ RETURNING TO THE BASE-LINE	+ IRREGULAR WAVE
POLY-SPIKES	<50µv	4	0	0	0
	50-100µV	7	0	0	1
	100-200µV	0	0	0	0
	>200µV	0	0	0	0

Fig. 37 Distribution of "poly-spike" group in the sample

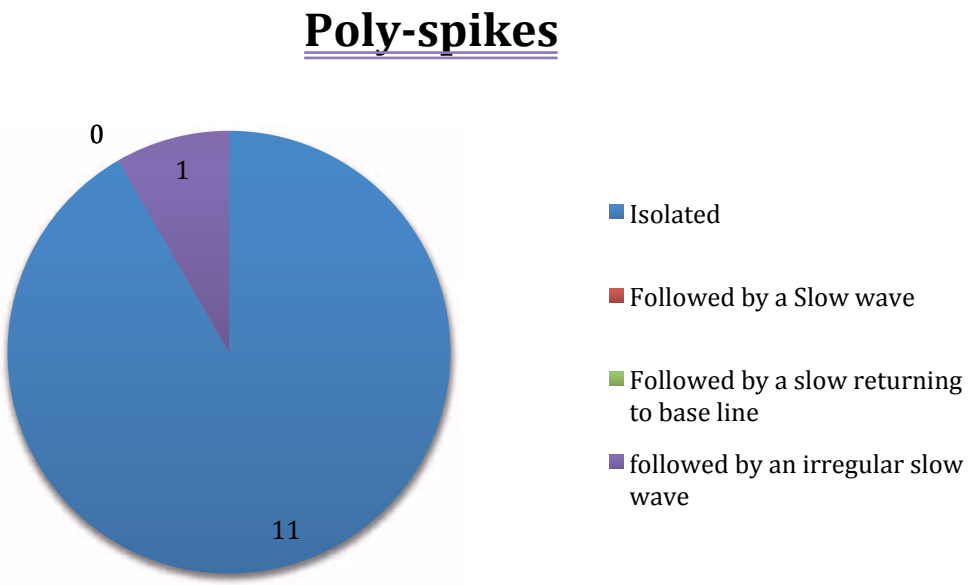


Fig. 38 EEG activity after "polyl spikes".

Regarding their amplitude, the most common voltage of the poly-spike group was of less than 50µV.

Amplitude

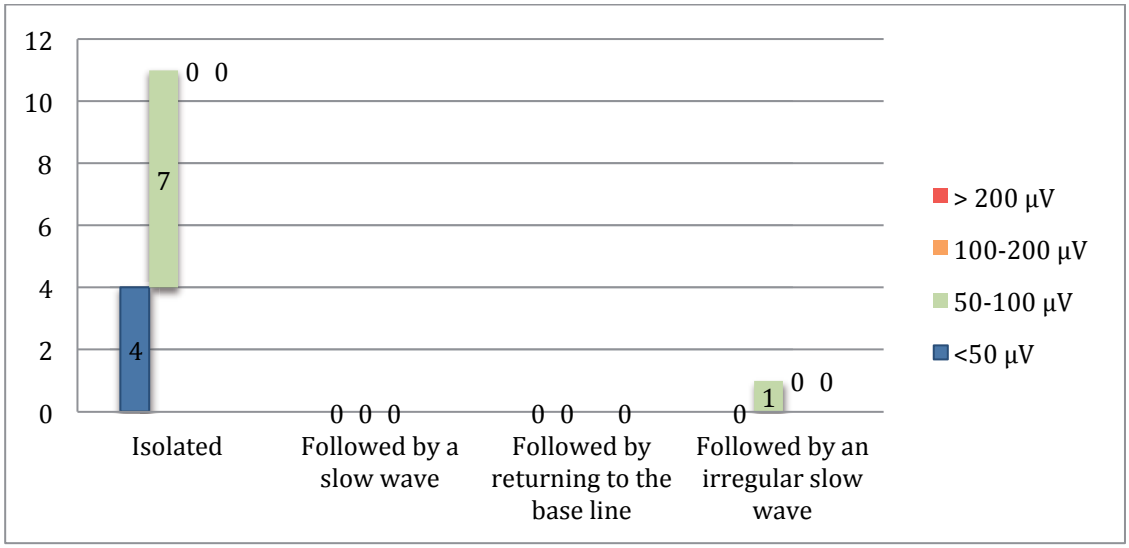
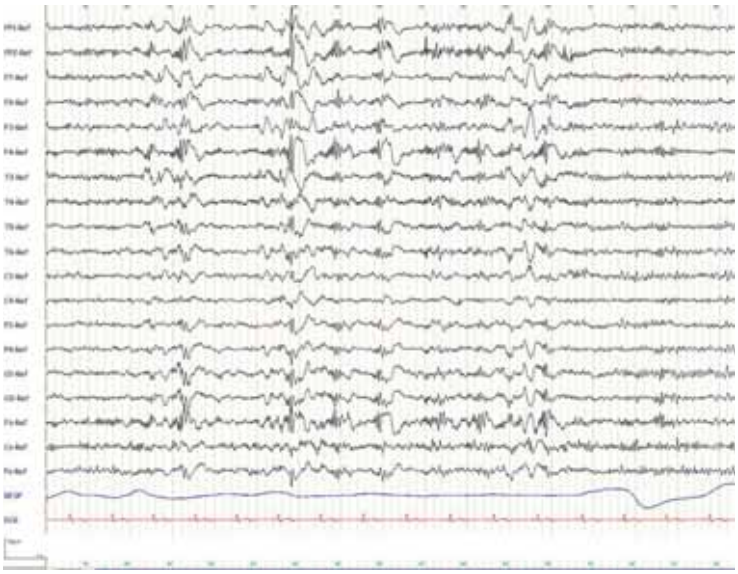


Fig. 39 Graphicaldescription of "polyl spikes" group, regarding the voltage.

Among the poly-spikes groups we only found isolated poly-spike waves, without a slow component afterwards. Only in one cases an irregular slow wave was found after the epileptiform discharge. All the epileptiform poly-spike activity had ad amplitude of less than 100 µV.

Graphical example of the possibilities within this category in the sample:

Isolated poly-spikes: We can see multiple spikes in right frontal regions.



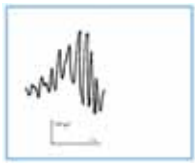


Fig. 40 Detailed view of poly-spikes waveform.

Fig. 41 Poly-spikes more expressive over right frontal regions, with maximal expression in F4 and diffusion to homologue and contralateral regions, Fp2, Fz, Fp1.

Poly-spikes followed by an irregular slow wave: We can see a poly-spike complex followed by a high amplitude irregular slow wave.

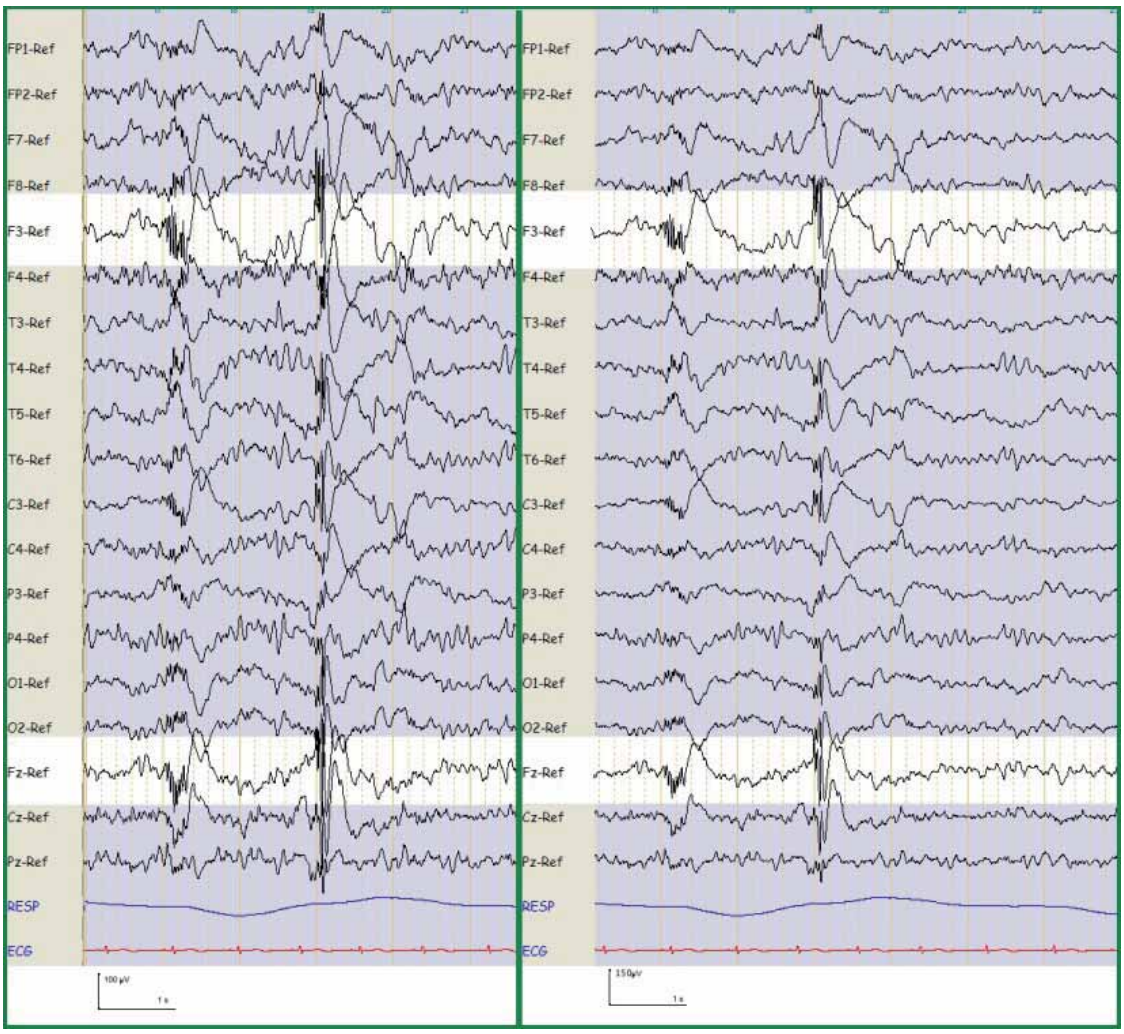


Fig. 42 Poly-spikes followed by an irregular slow wave with maximal expression in left frontal regions; maximal expression in F3 and diffusion especially to Fz, F7, Fp1, T3, C3.Comparative view in a referential montage with different voltage settings (10µV/mm and 15µV/mm).

- **"Irregular slow wave":** This category encloses unspecific waves that usually are seen added to other specific epileptic waves.

By definition it is delta wave so there is no followed by another slow component, and there appear isolated in the sample, as we can see in the table below.

INTERICTAL EEG MORPHOLOGY		ISOLATED	+ SLOW WAVE	+ RETURNING TO THE BASE-LINE
IRREGULAR SLOW WAVE	<50µv	9	0	0
	50-100µV	25	0	0
	100-200µV	10	0	0
	>200µV	1	0	0

Fig. 43 Distribution of "irregular slow wave " group in the sample.

Regarding the amplitude, the most common voltage was of 50-100 µV, as we can see in the graphic below:

Amplitude

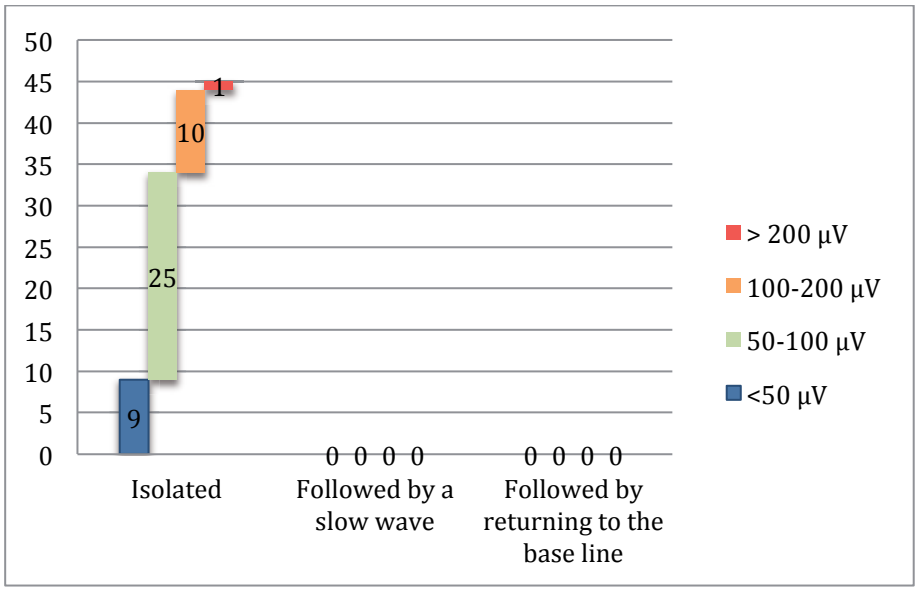


Fig. 44 Graphical description of "irregular slow wave" group, regarding the voltage.

Graphical example in the sample:

Isolated irregular slow wave:

All irregular slow waves were found isolated of after another waveform (already seen in the previous groups of specific epileptic interictal activity.

They show the abnormal function of the region, being unspecific waves that accompany the specific epileptiform waves, as diphasic sharp waves or spikes.

There were only four cases[14] in which irregular slow waves were the only wave found as interictal activity. In one of them[15] we recorded two seizures during hyperventilation. The other three had clinical history of seizures and all of them had a clear traumatic antecedent.

Most of them had amplitude of 50-100 μV, as in the picture below:

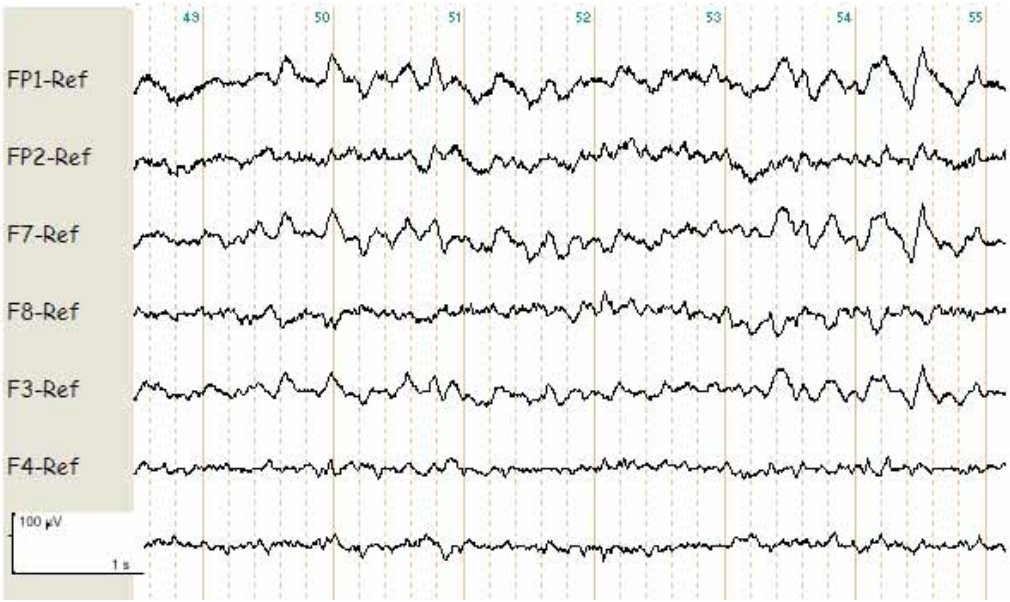


Fig. 45 Irregular slow waves in left frontal regions, Fp1, F7, F3.

[14]Cases 23, 97, 104 and 164.
[15] Case 104

c) Overall distribution by morphology

As we can see in the picture, the most common waveform in the overall distribution is “sharp wave”, followed by “spike”, “irregular slow wave”, “diphasic sharp wave” and “poly-spikes” respectively.

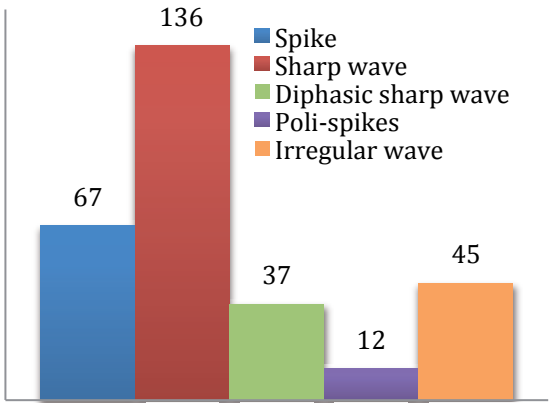


Fig. 46 Overall distribution by morphology.

The different categories do not have equally distribution when amplitude is considered, as one type of waveform is more common at a specific amplitude value. The distribution regarding morphology and amplitude is showed in the next graphic.

Overall distribution by morphology and amplitude

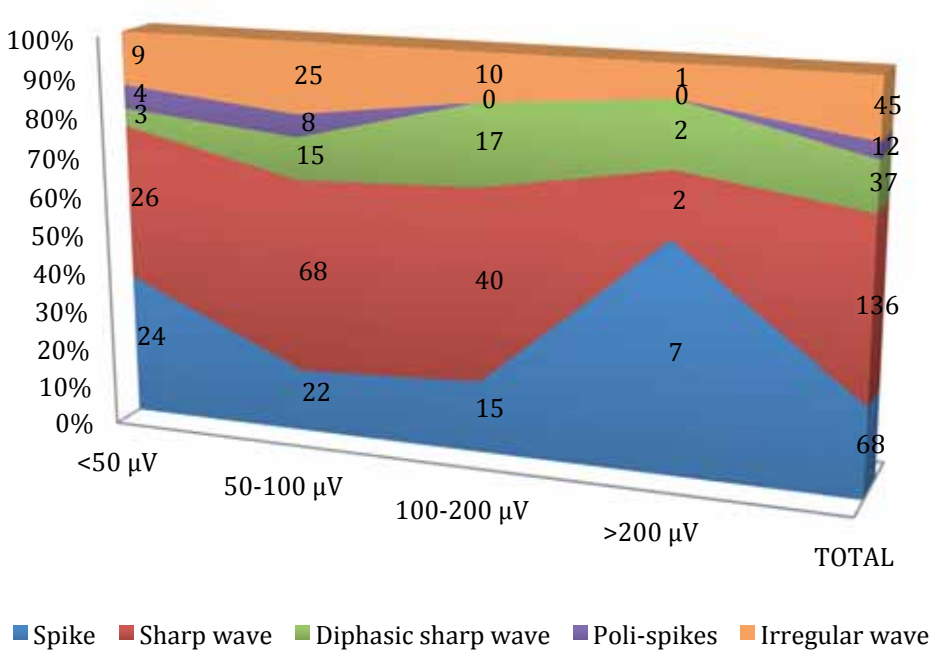


Fig. 47 Distribution by morphology and amplitude.

As we have seen in the graphic, “Sharp wave” is the most common morphology for all the amplitudes except for the group of more than 200 μV. The “diphasic sharp wave” increases at interval of 100-200 μV, and the “spike” is the most common one at very high voltage (more than 200μV).

We can group both “sharp wave” and “diphasic sharp wave” as subgroups of the same waveform regarding its duration, being both of them part of the same spectrum of waves of 70-200 ms. of duration. Whether the wave is simple or diphasic provides more specific information about our sample. Grouping both of the subgroups, the distribution and the distribution regarding its voltage is shown in the next three graphics:

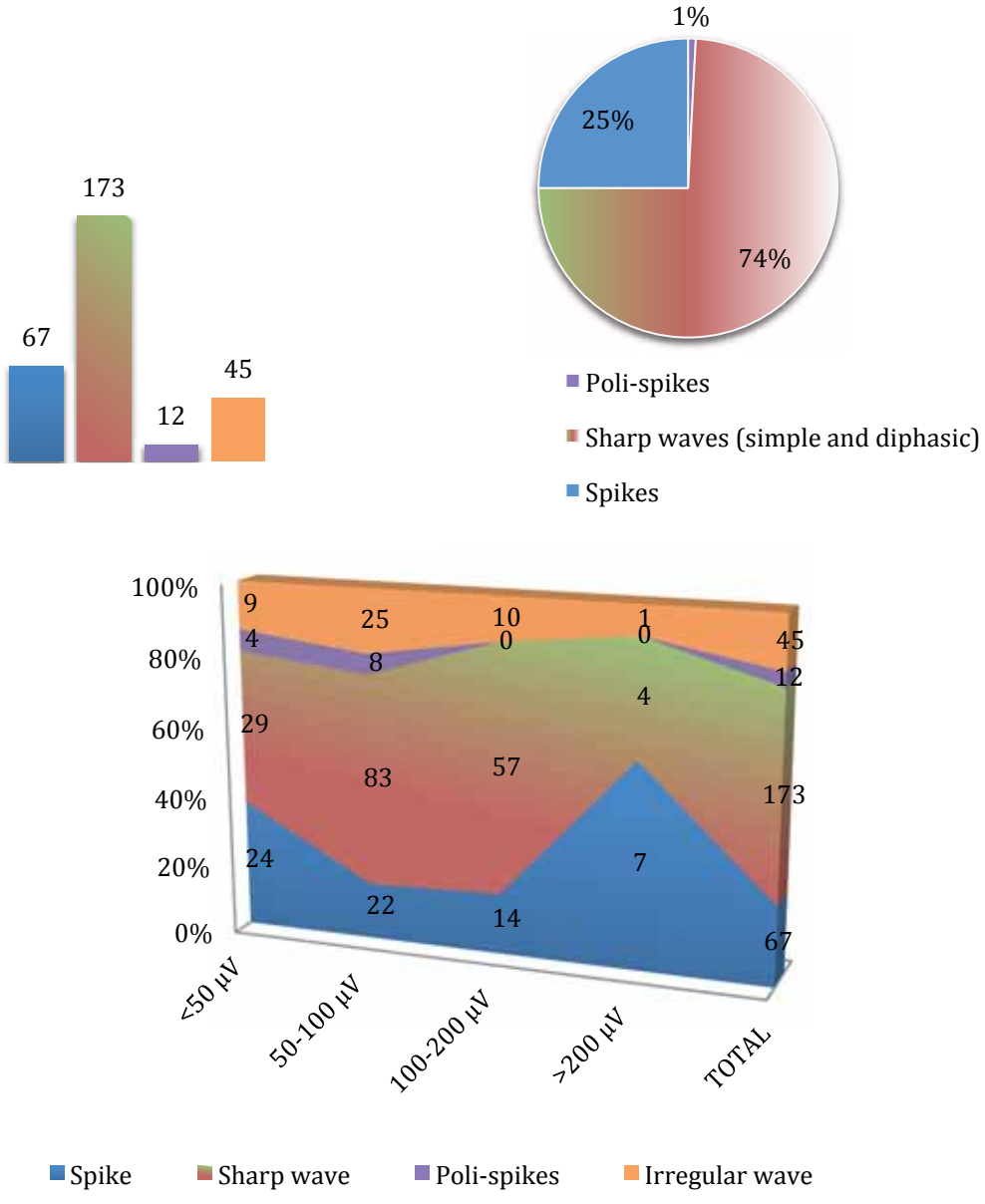


Fig. 48 Distribuion by morphology, grouping sharp and diphasic sharp waves.

A detail we must take into account is that one patient usually has several data points regarding the three axes classification explained. But when analysing the data points for each patient we can see that 119 out of the 175, which constituted the 68% of the cases, maintained the data points within a single waveform category:

The graphic shows the distribution of the cases which maintained the same waveform category in spite of having several data points, which would mean changes in amplitude or regarding the following EEG activity, according to the classification used.

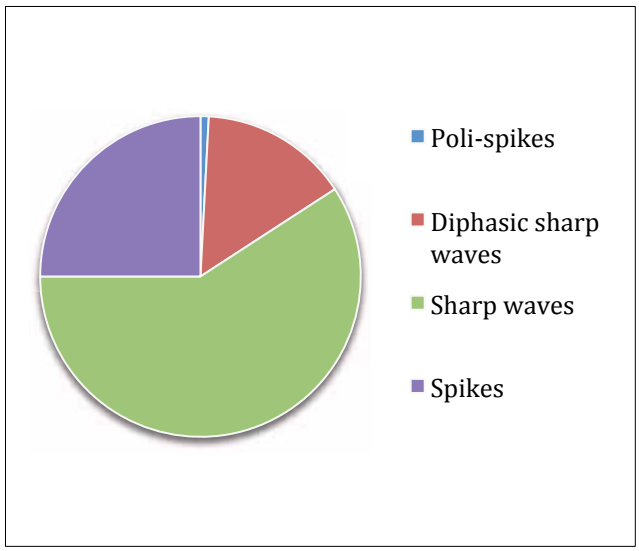


Fig. 49 Morphology of cases with the same group wave within all EEG recordings.

6.2.2 Ictal activity

We recorded at least one seizure in 51 out of 175 patients, which constitutes 28.9% of the cases.

a) Onset location: assessment of the most active electrode at seizure onset whenever possible.

Each recorded and selected seizure was studied to assess the most active electrode at onset, looking for the already described EEG features at onset.

Some cases are codified as unspecific in two situations: when the most active electrode was not enough clear and in cases recorded on paper, when the electrode setting was not enough accurate to define an specific electrode[16].

[16] For instance, sometimes the electrode settings used for the recording on paper did not include F7 and F8, so those cases were codified as "unspecific". Nevertheless, if the recording was clear enough to assess the hemisphere, the lateralization was codified (left and right).

Fp1	Fp2	F3	F4	F7	F8	Fz	Left unspecific	Right unspecific	
5	4	6	4	8	5	1	5	5	
Pre frontal.		Central-f.		Inferior f.		Midline	Defined by side		Unspecific
9		10		13		1	10		8

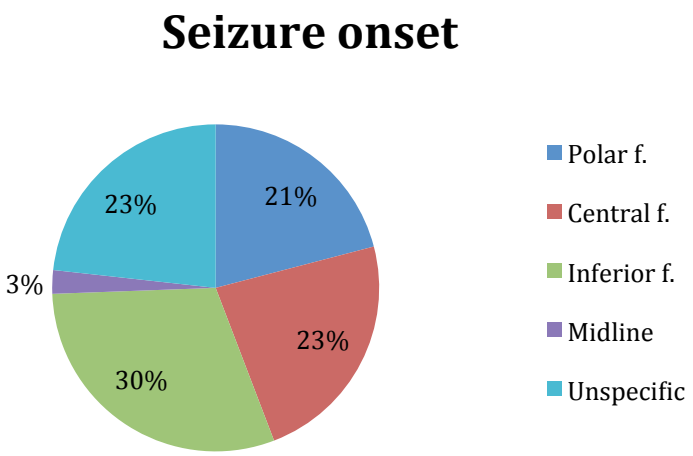


Fig. 50 Distribution of location of seizure onset as a percentage of the total of recorded seizures.

We can see that the inferior frontal regions are slightly more frequent as location of onset than the rest regions of the frontal lobe.

b) Frequencies at seizure onset

In the picture below we can see that the sooner at seizure onset, the faster the observed frequency is. As seizure progresses the frequency of the waves tend to slow progressively.

The band of beta frequency was the most frequently seen in the sample at seizure onset.

The distribution of the first observed frequency at seizure onset is the following:

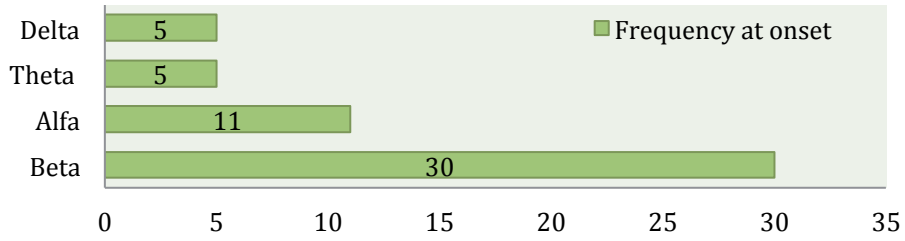


Fig. 51 Frequencies at seizure onset.

From a beta frequency at onset, there is a progressive slowing of frequencies from the beginning of the seizure.

We can see the mean of the first three observed frequencies from seizure onset:

Graphical description of the 1st, 2nd and 3th observed frequencies during the seizures

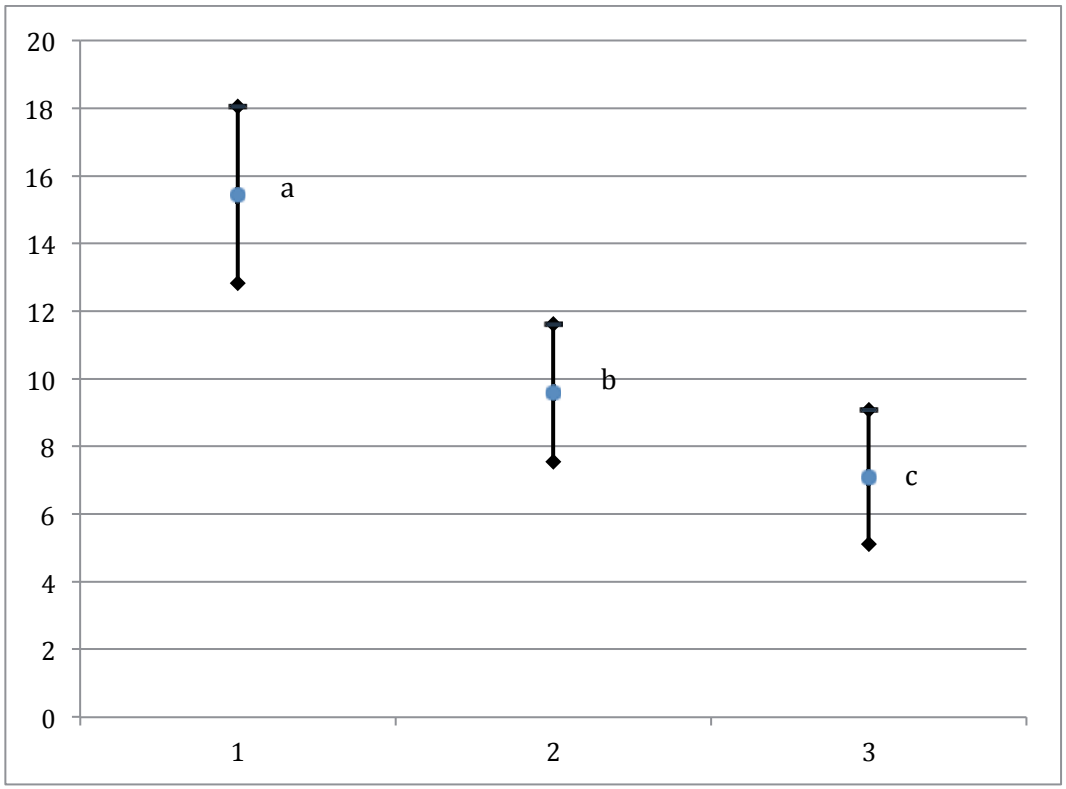


Fig. 52 Mean values for the three first frequencies during the seizures, mean and CI 95%.

These differences in frequency have statistical significance (see statistical description and the detail of the analysis).

For complementing this view, the next graphic shows the relative duration of the three first frequency observed.

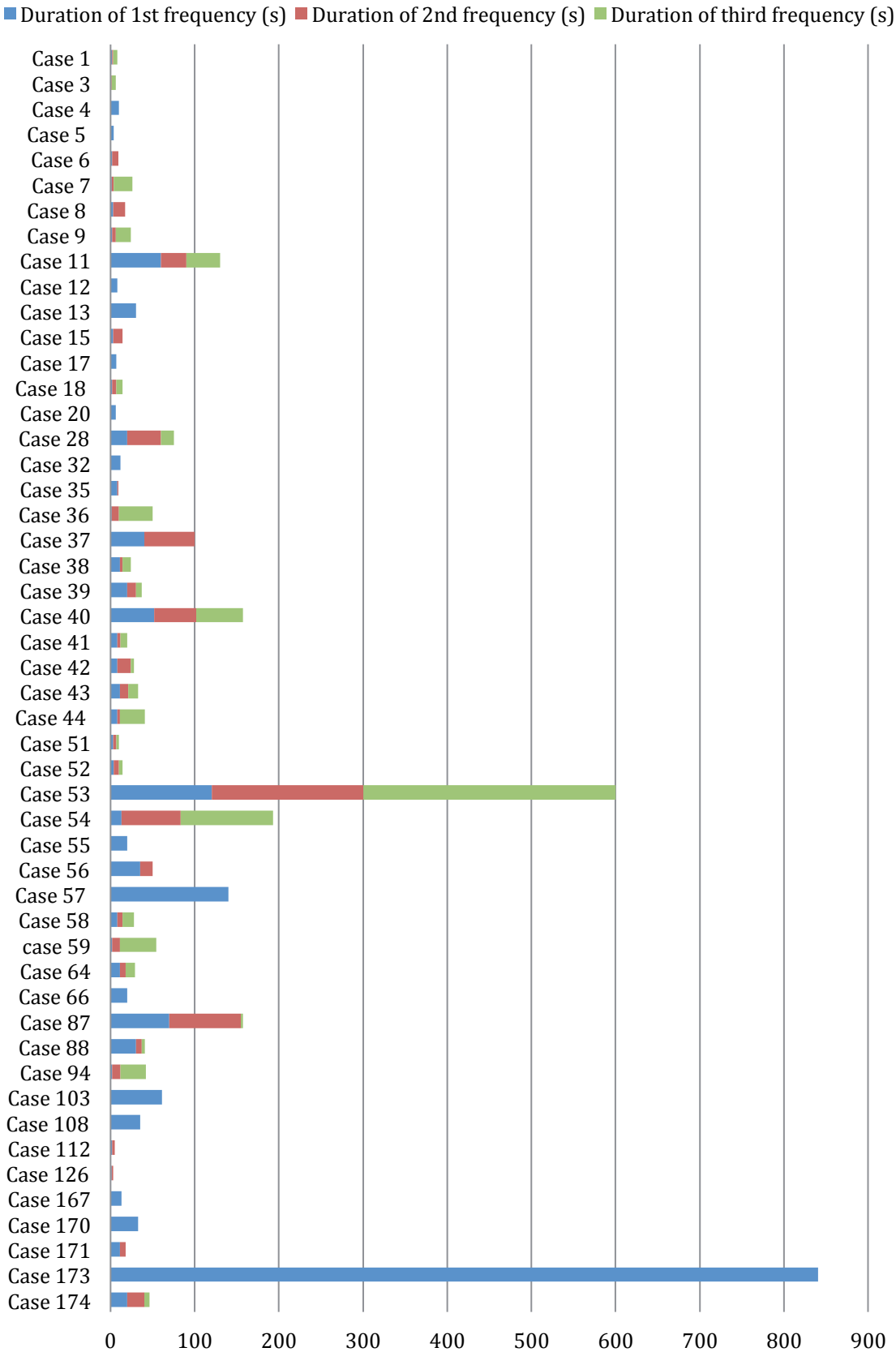


Fig. 53 Graphical description of the relative duration of the three first frequencies observed during seizures.

As it is shown in the previous graphic, Case 53 and 173 have a much longer duration than the rest of the seizures. To see in detail the graphic for all the rest of the cases, here is the same graphic without these two cases:

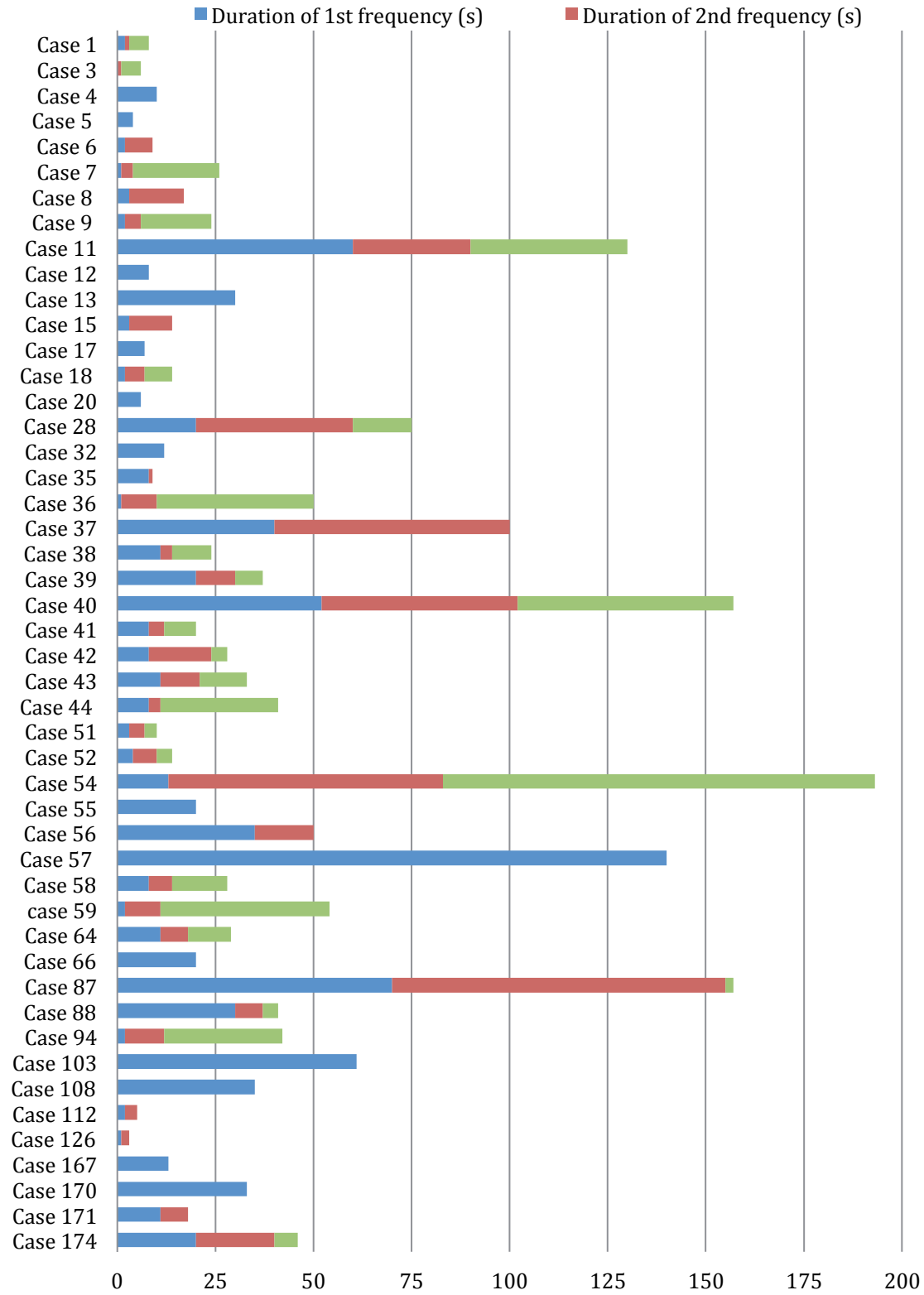


Fig. 54 Graphic showing the relative duration of the first three frequencies excluding cases 53 and 173.

As it is shown in the previous graphic most of the all three morphology (82%) lasted less than 75 seconds there are still some cases with a duration that exceeds that duration, so We exclude the cases 11, 37, 40, 54, 57 and 87 to see with more detail the majority of the seizures.

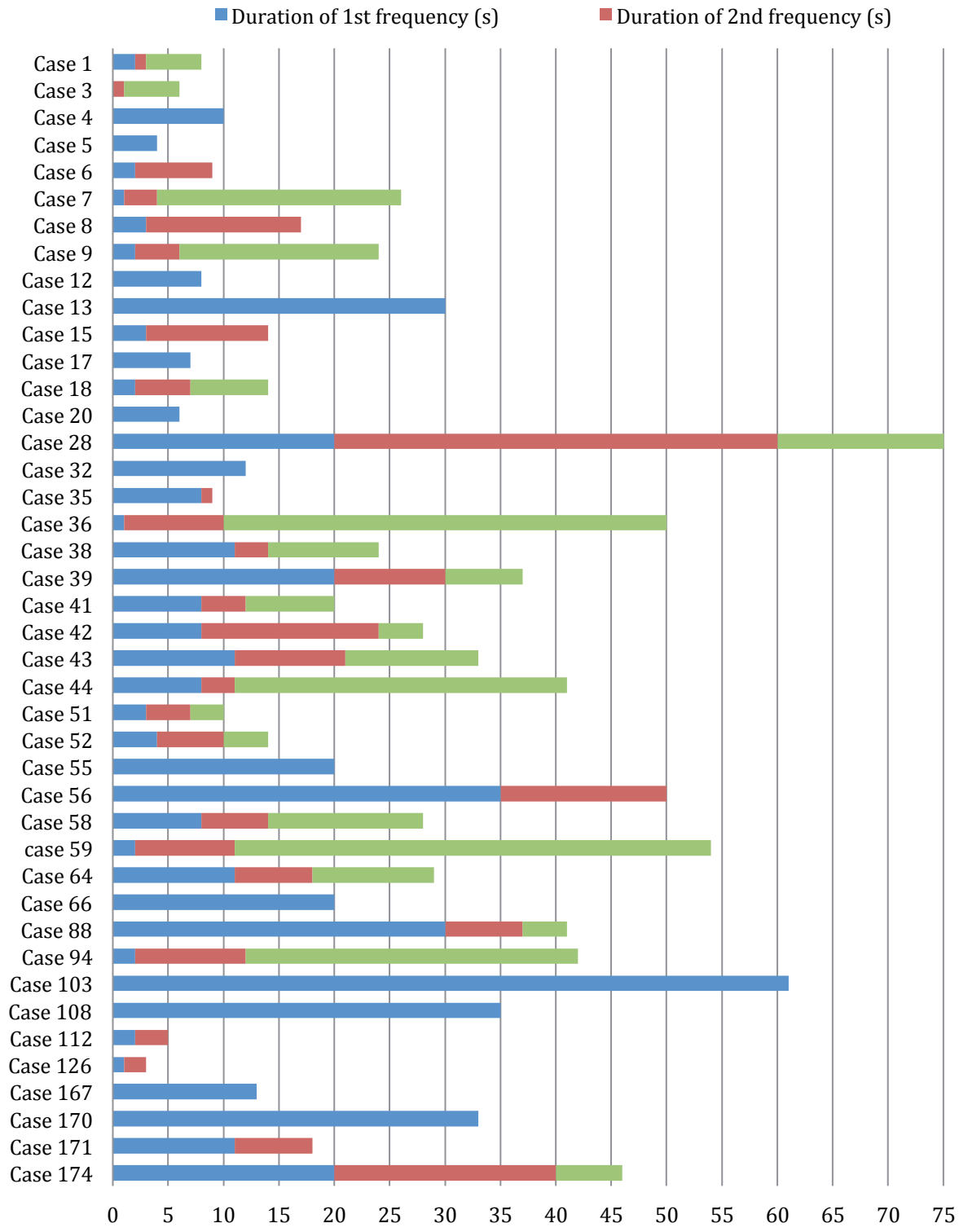


Fig. 55 Duration of seizures, in "seconds". Most of seizures were shorter tan 50 seconds, as we can see in the graphical distribution.

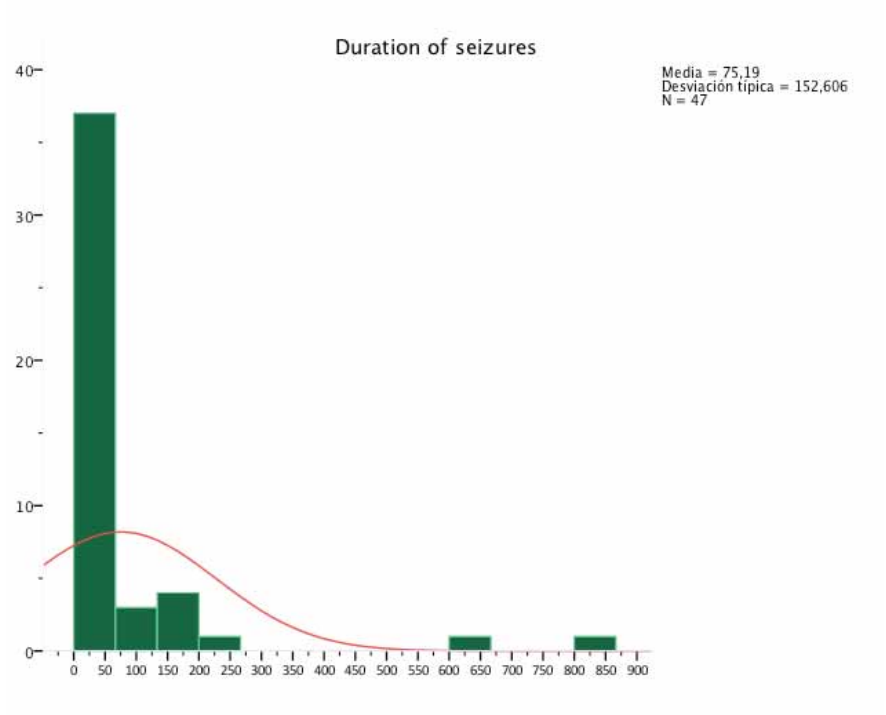


Fig. 56 Duration of seizures. Distribution of the sample.

The mean duration of seizure is 75 seconds, having ictal activity as short as 3 seconds and up to a maximal duration of 14 minutes. The quartiles are: percentile 25= 10 seconds, percentile 50= 24 seconds, and percentile 75= 90 seconds.

c) Morphology at seizure onset:

To perform a detailed and in-depth morphological analyses of the seizure onset activity it was necessary to consider what aspects were common among several seizures which could be interesting for grouping the seizures regarding them.

Once done these analyses, a new morphological classification for frontal seizures is proposed regarding the electroencephalographic characteristics.

EEG onset was analysed regarding the waveforms at onset and its amplitude resulting four categories that enclose all the seizures of the sample.

This classification differentiates four possible categories for seizure onset:

1- Synchronized rhythm without a prominent change in amplitude
2- Low amplitude synchronized rhythm
3- Attenuation
4- Spike/sharp wave within a slow wave just befor the syncronized rhythm

The most frequent characteristic at seizure onset was a synchronized rhythm without a prominent change in amplitude, followed by a low amplitude synchronized rhythm.

Some cases had such a diminution of amplitude that was codified in the third category, being the attenuation of amplitude their main morphologic characteristic at onset.

Even less cases presented a sharp wave within a slow wave, being an odd characteristic as a main feature at seizure onset in the sample.

We can see in the following graphic the distribution of morphological ictal pattern at onset:

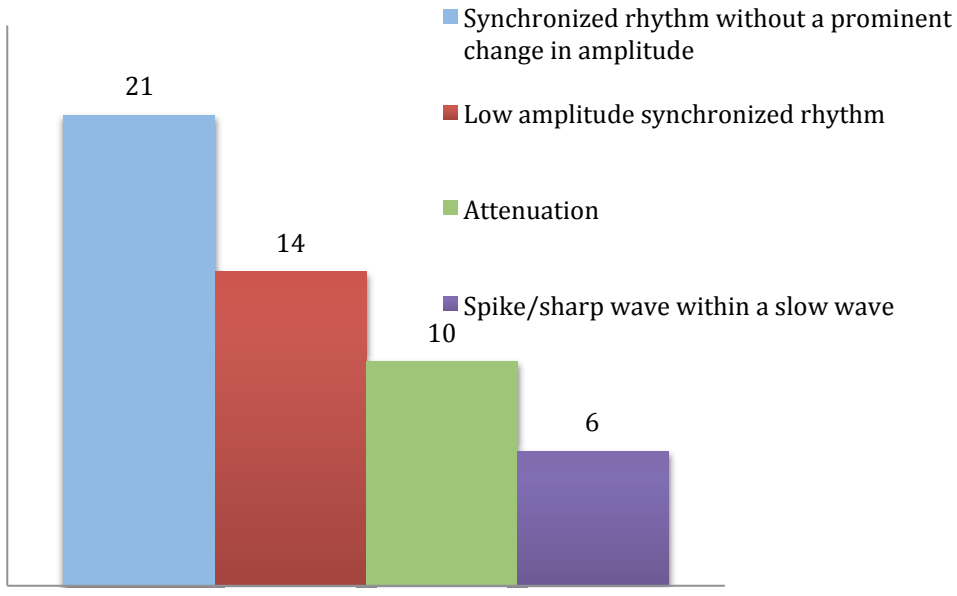


Fig. 57 Morphological electroencephalographic characteristics at seizure onset.

All the recorded seizures were classified according to this classification, so we propose its application in the daily practice of EEG, for frontal lobe seizures:

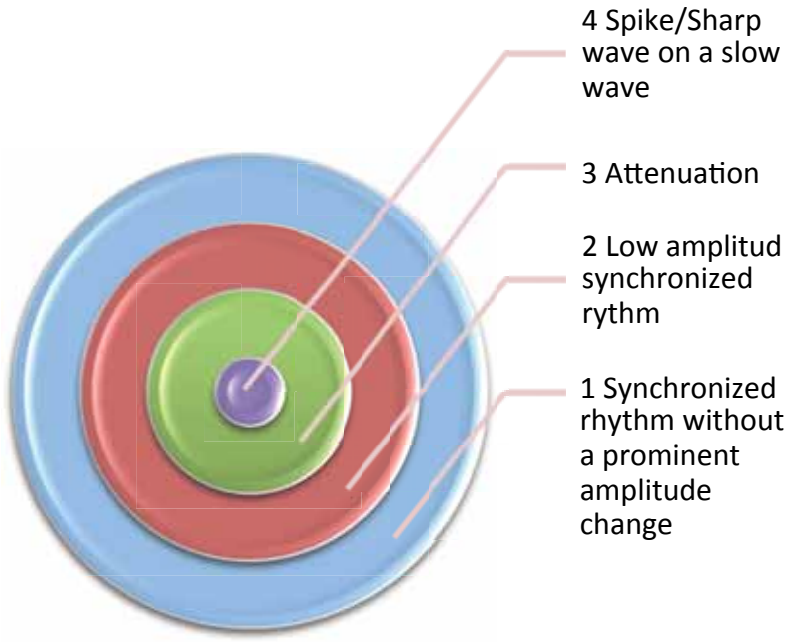


Fig. 58 Morphological categories at seizure onset.

The category with more cases in the sample is linked to the biggest circle of the figure, and the category with less number of cases with the smallest one.

❖ Synchronized rhythm without a prominent change in amplitude

22 out of 51 cases had a synchronized rhythm as the main EEG feature at seizure onset, the most frequent pattern at seizure onset.

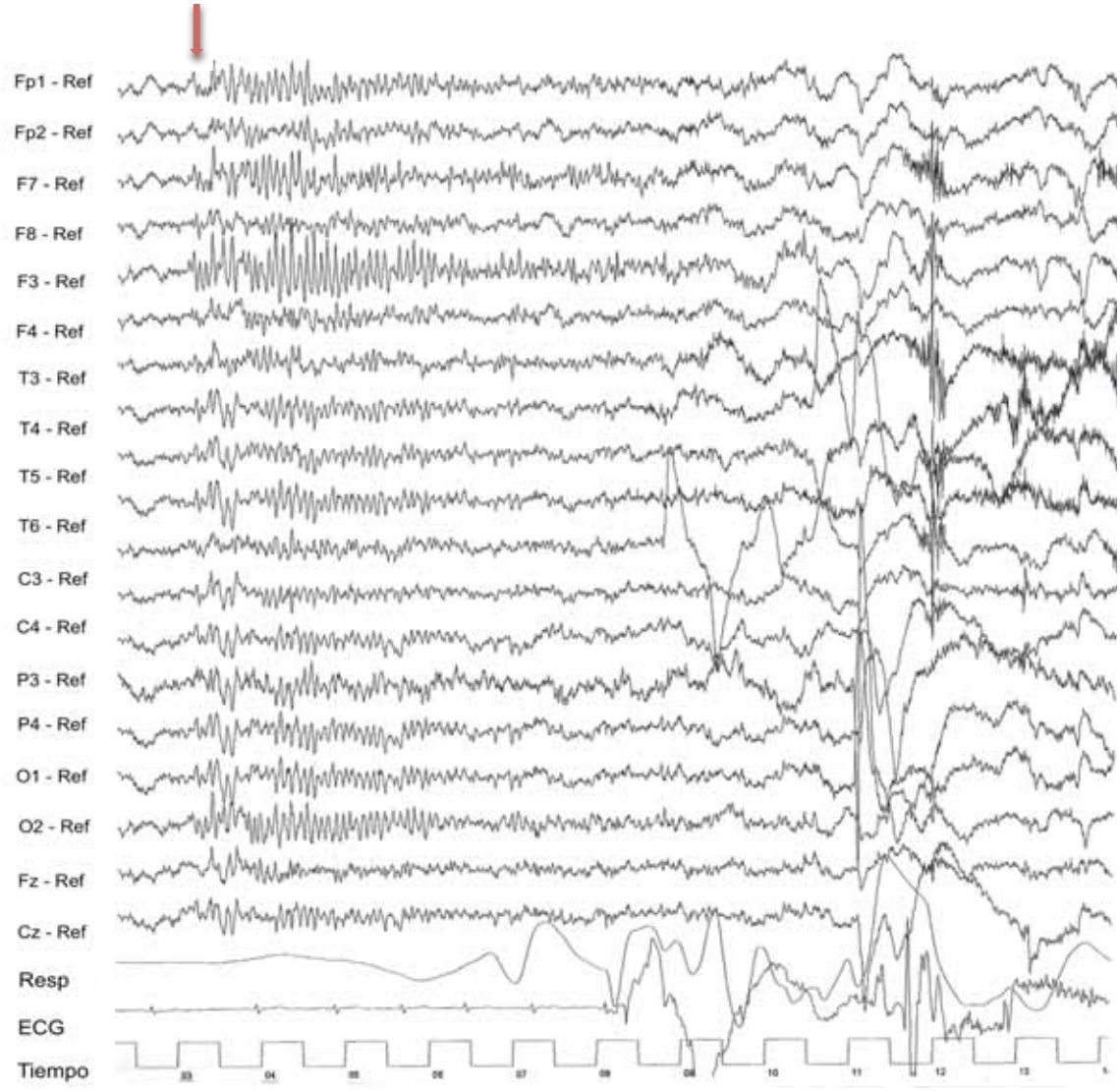


Fig. 59 Case 4. We can see a medium-high amplitude synchronized rhythm with maximal expression en left front-central region, F3, and diffusion to the rest of the electrodes, especially to F7, Fp1 and remarkable to contralateral posterior region, O2.

❖ Low amplitude synchronized rhythm

A fixed rhythm with low amplitude was the second most common morphological feature at seizure onset, followed in some cases by attenuation or by the continuation of a synchronized rhythm with higher amplitude (6/16 for both possibilities).

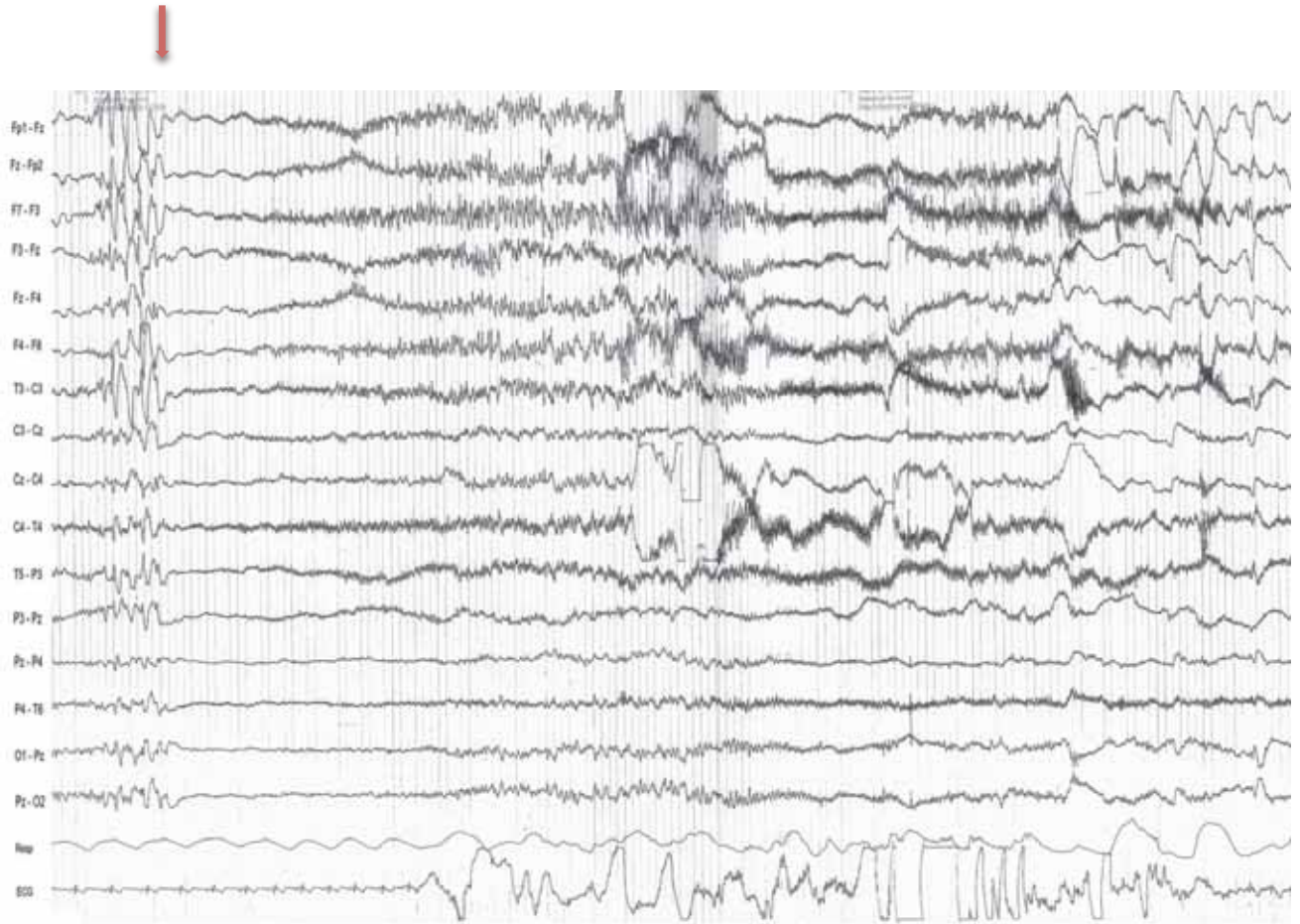


Fig. 60 In this figure we can see a low amplitude synchronized rhythm that progressively increases in amplitude in right frontal regions, starting with a brief attenuation just at the beginning of the ictal activity.

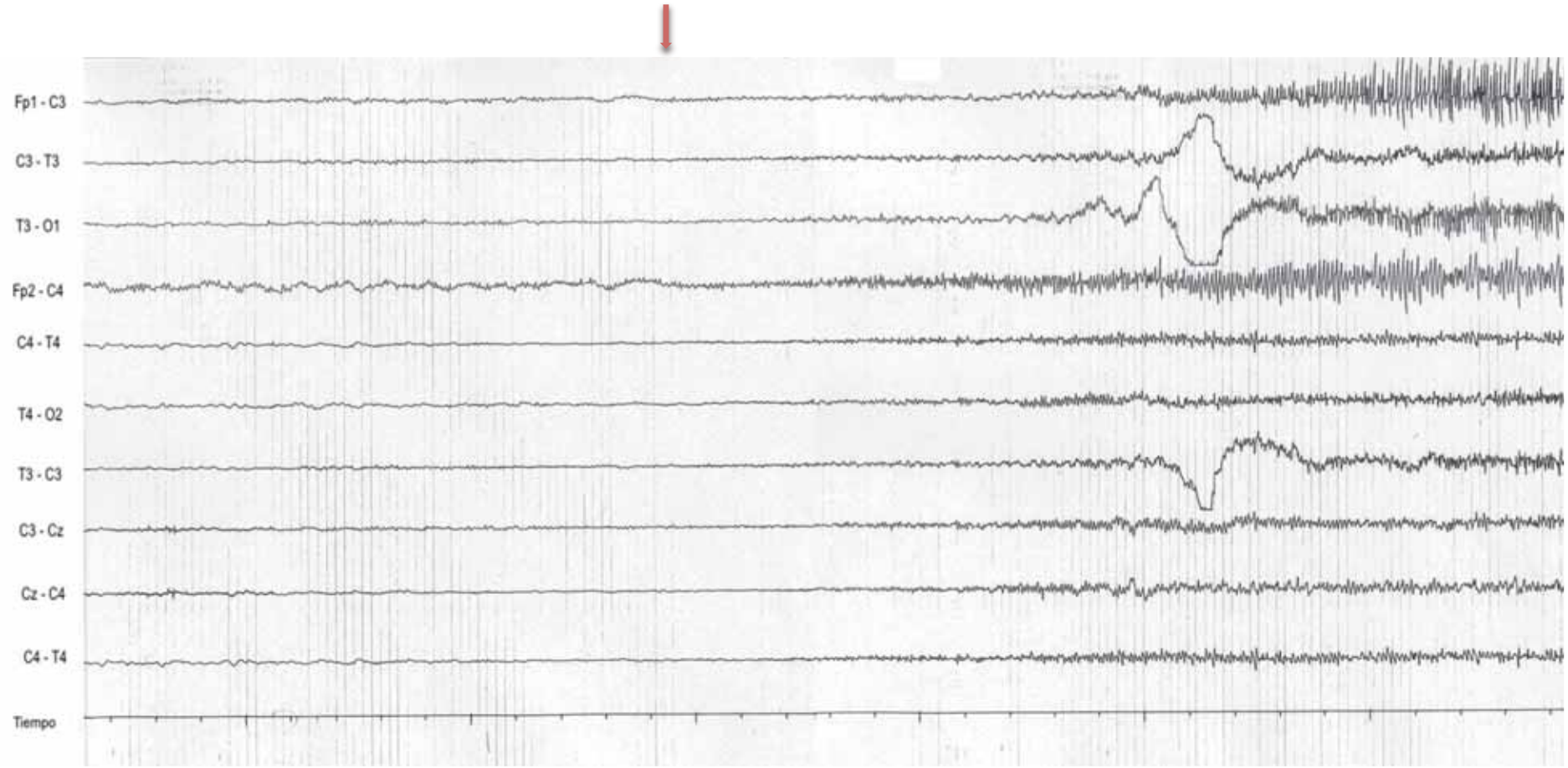


Fig. 61 Seizure onset characterized by a fix and low amplitude synchronized rhythm. We can see some slow waves with maximal expression in right prefrontal region (Fp2-C4), which are interrupted by an attenuation and immediate fixed synchronized rhythm arising from this region.

❖ Attenuation

Six cases showed attenuation as the main morphological EEG feature at seizure onset. We can see in the following example how the EEG activity attenuates and it is followed by a synchronized increasing amplitude synchronized rhythm. We will analyse this case later on, describing the interictal and ictal activity in detail (5, 2.3).

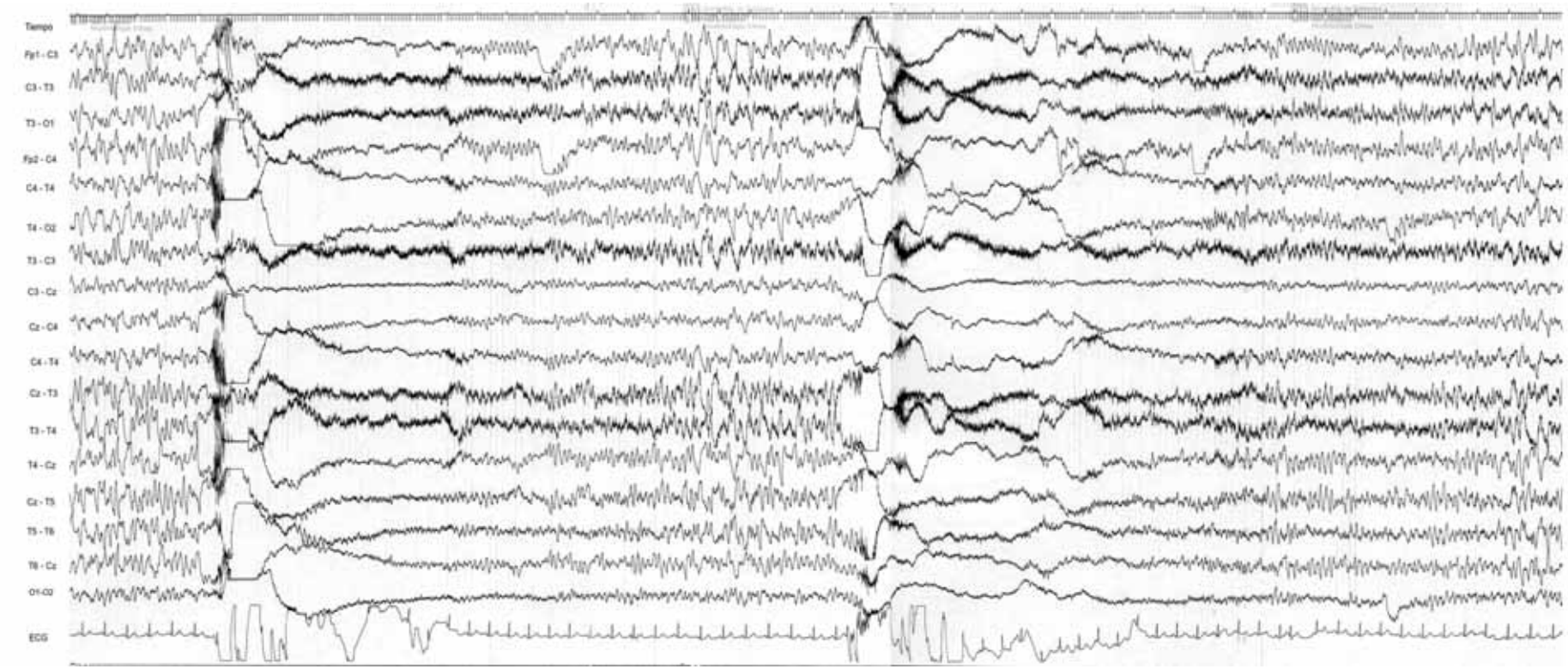


Fig. 62 Two seizures with global attenuation at seizure onset and progressive identification of the ictal rhythm.

❖ Spike/sharp wave within a slow wave

The last group observed regarding EEG morphology at seizure onset was a spike or sharp wave lying within a slow wave. Six cases had seizure with this characteristic. To illustrate the group, we can see in Fig. 58 and 59 this feature at 10μV/mm and 15μV/mm respectively.

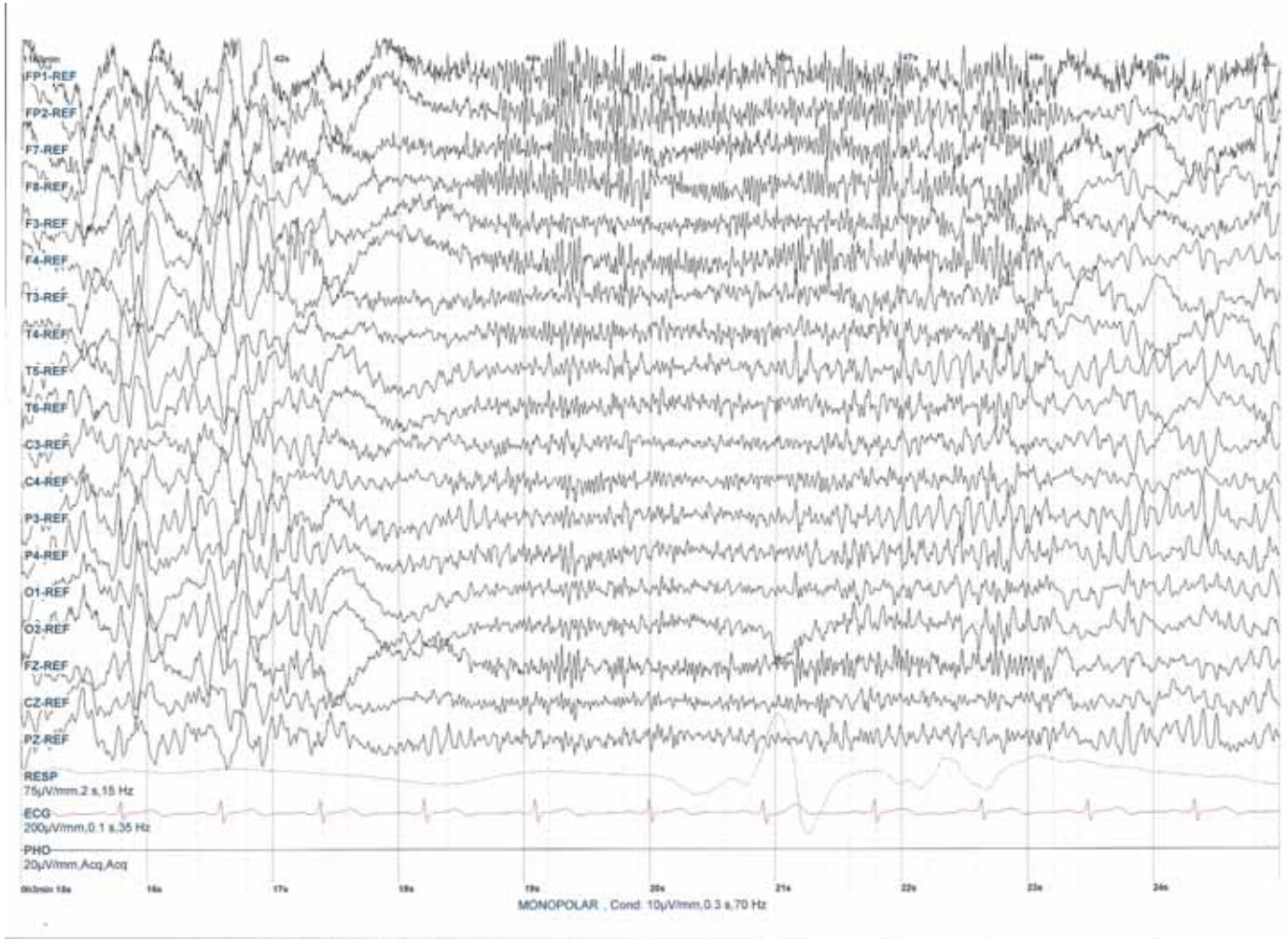


Fig. 63 Sharp waves within a slow wave in right front central region (F4), at 10μV/mm, just before/at seizure onset.

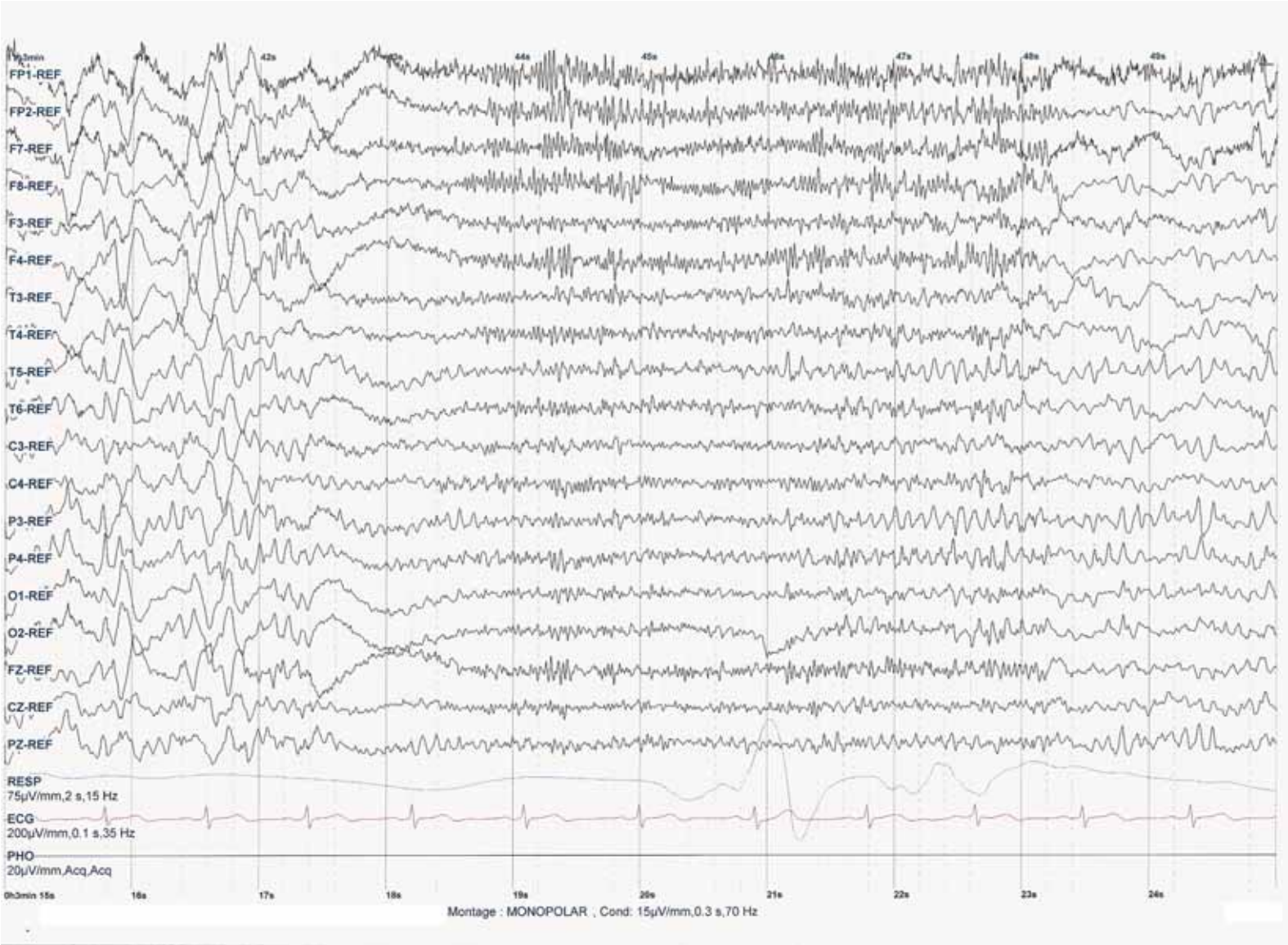


Fig. 64 Same picture with sensibility of 15µV/mm, for more detailed view. Sharp waves just before/at seizure onset with maximal expression in F4.

6.2.3 A graphical point of view of some interesting cases representative of the sample

Now we have analysed different aspect of the interictal and ictal epileptiform activity of the sample we are going to comment some practical aspect in which we will take into account the morphological aspects previously studied.

When reading an EEG recording, after the study of the background activity we should look for interictal epileptiform activity standing out from the background. Sometimes it is localized and easily detectable, but some other times, it is difficult to identify, due to an unusual morphology or to a wide diffusion of the activity, etc. which can make precise diagnostic a real challenge.

From a practical point of view of the EEG reader you need to be capable of change different aspects of the recording in order to get the clue of the activity you are looking at. This is a challenge in frontal lobe epilepsy.

Interictal epileptiform activity can appear very well located but many times appear more widespread;

When the epileptiform activity appears diffusely, we use different tools to approach to the recording: Settings of electrodes, sensitivity and seconds per page.

We can use different electrode settings (montages) to review the EEG, and each of them will provide some useful information in the reviewing. At the same time, each montage has its disadvantages. The reviewer must know what to expect of the different montages to be able to extract as much information as possible from each.

Some of the most used montages in our lab are the following:

Montages	Referential	Standard bipolar	Transversal bipolar	Longitudinal bipolar	Triangular bipolar	Circular bipolar
Channel 1	Fp1-Ave	Fp1-C3	Fp1-Fz	Fp1-F3	Cz-Fp1	Fp1-T3
Channel 2	Fp2-Ave	C3-T3	Fz-Fp2	F3-C3	Fp1-Fp2	T3-O1
Channel 3	F7-Ave	T3-O1	F7-F3	C3-P3	Fp2-Cz	O1-O2
Channel 4	F8-Ave	Fp2-C4	F3-Fz	P3-O1	Cz-F7	O2-T4
Channel 5	F3-Ave	C4-T4	Fz-F4	Fp2-F4	F7-F8	T4-Fp2
Channel 6	F4-Ave	T4-O2	F4-F8	F4-C4	F8-Cz	Fp1-F7
Channel 7	T3-Ave	T3-C3	T3-C3	C4-P4	Cz-F3	F7-T3
Channel 8	T4-Ave	C3-Cz	C3-Cz	Fz-Cz	F3-F4	T3-T5
Channel9	T5-Ave	Cz-C4	Cz-C4	Fp1-F7	F4-Cz	T5-O1
Channel 10	T6-Ave	C4-T4	C4-T4	F7-T3	Cz-T3	Fp2-F8
Channel 11	C3-Ave	Cz-T5	T5-P3	T3-T5	T3-T4	F8-T4
Channel 12	C4-Ave	T5-T6	P3-Pz	T5-O1	T4-Cz	T4-T6
Channel 13	P3-Ave	T6-Cz	Pz-P4	Fp2-F8	Cz-T5	T6-O2
Channel 14	P4-Ave	Cz-O1	P4-T6	F4-T4	T5-T6	Cz-C3
Channel 15	O1-Ave	Cz-O2	O1-Pz	T4-T6	T6-Cz	C3-C4
Channel 16	O2-Ave	O2-Cz	Pz-O2	T6-O2	Cz-O1	C4-Cz
Channel 17	Fz-Ave				O1-O2	
Channel 18	Cz-Ave				O2-Cz	
Channel 19	Pz-Ave					

By using some of the previous montages described, we intend to know the location of the focus and characterize the ictal onset when a seizure is recorded.

First of all we will see the pictures of an easily locating focal frontal interictal activity and afterwards we will analyse a more difficult EEG recording, with more diffusion of the focal activity, and we will comment the tools we can use to get to know where the epileptiform activity is sourcing from.

a) Well located interictal activity

Fig. 65 shows very well located short sharp waves in right pre-frontal region, Fp2, both in bipolar and in referential montages. It spreads very little, only towards adjacent region (inferior frontal, F8).

Many times the focal activity is not so well localized and comes out as “generalized” or, better said, widespread diffuse. In those cases we would need to change montages several times to asses that the activity we are l looking at is, in fact, focal.

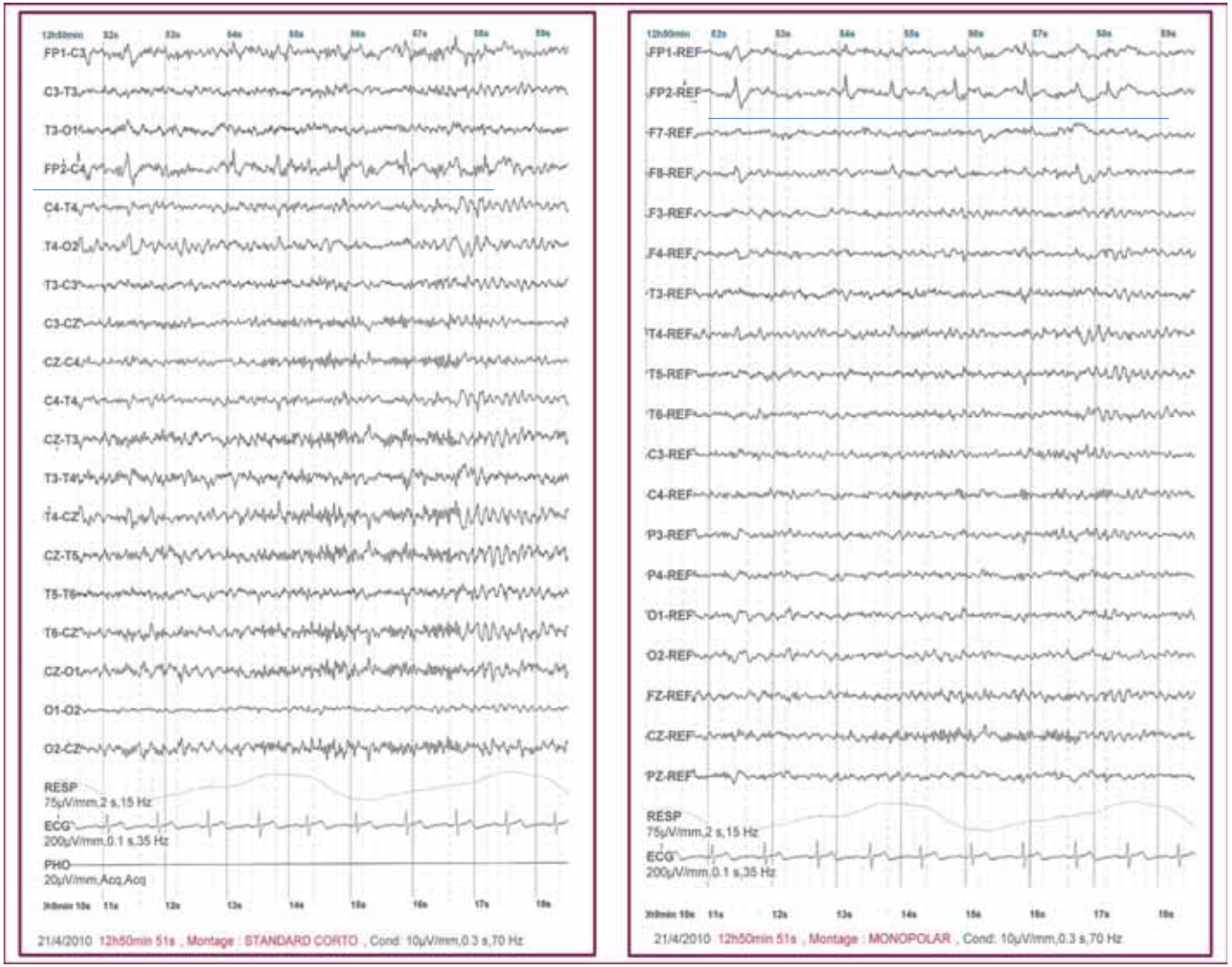


Fig. 65 Case 15. Comparing the same epoch in bipolar and referential montage. Maximal expression of IED in Fp2.

b) Widespread interictal epileptiform activity. The importance of using several electrode settings

Fig. 66 shows an example of epileptiform activity that spreads much more.

In a “standard” bipolar montage with sensitivity of 10µV/mm we can see a widespread paroxysm. We might be able to notice left-side predominance in the expression of the paroxistic interictal activity.

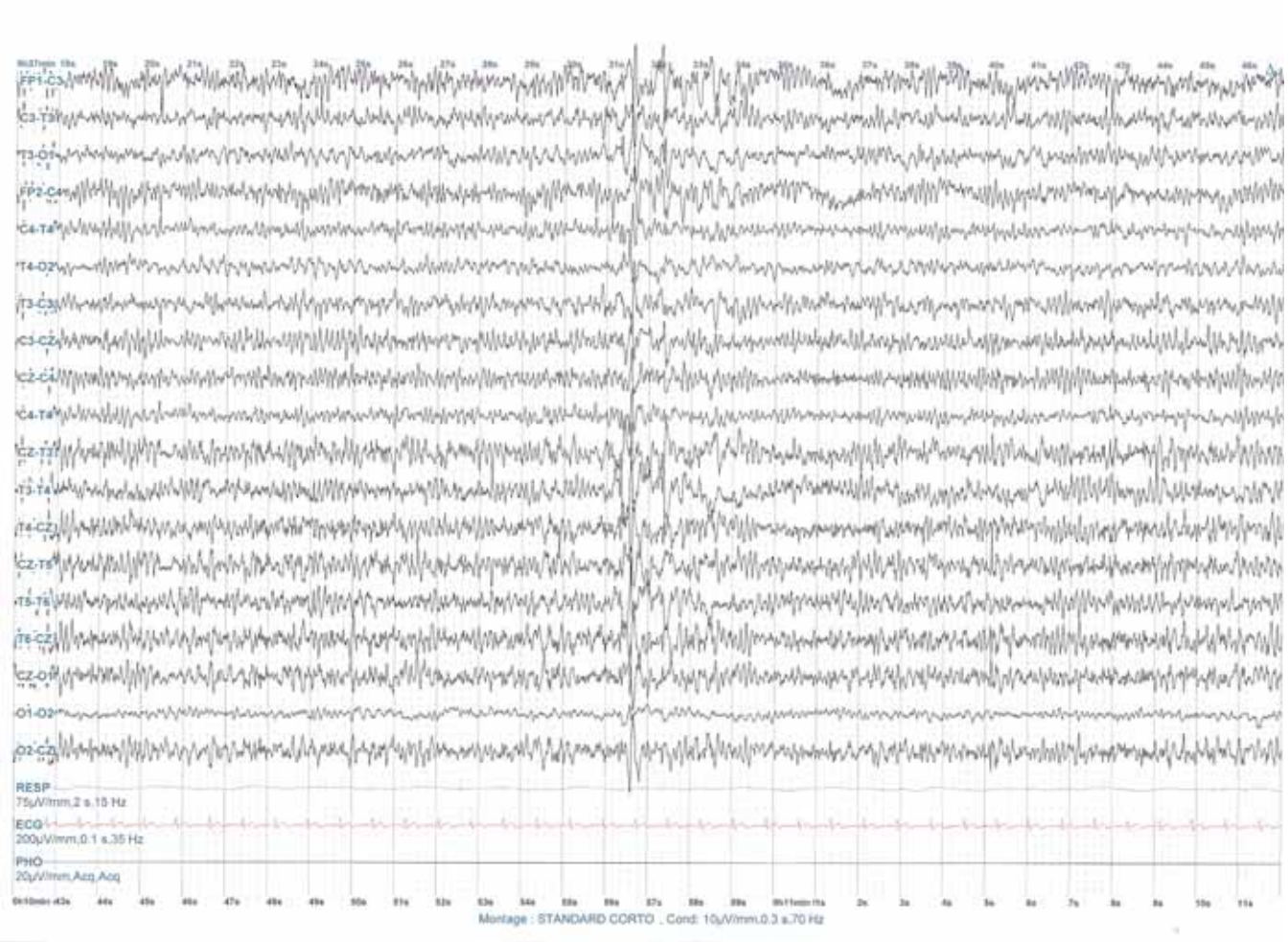


Fig. 66 Bipolar montage. Paroxistic activity without a clear location at 10µV/mm.

If we look the same epoch with less sensitivity, we see in Fig.67 (15µV/mm) a left-sided predominance of irregular short waves much more clearly than in the previous picture.

To extract further information about the epileptiform activity we can see how it looks in another bipolar montage first (Fig. 68) and in a referential montage (Fig. 69).

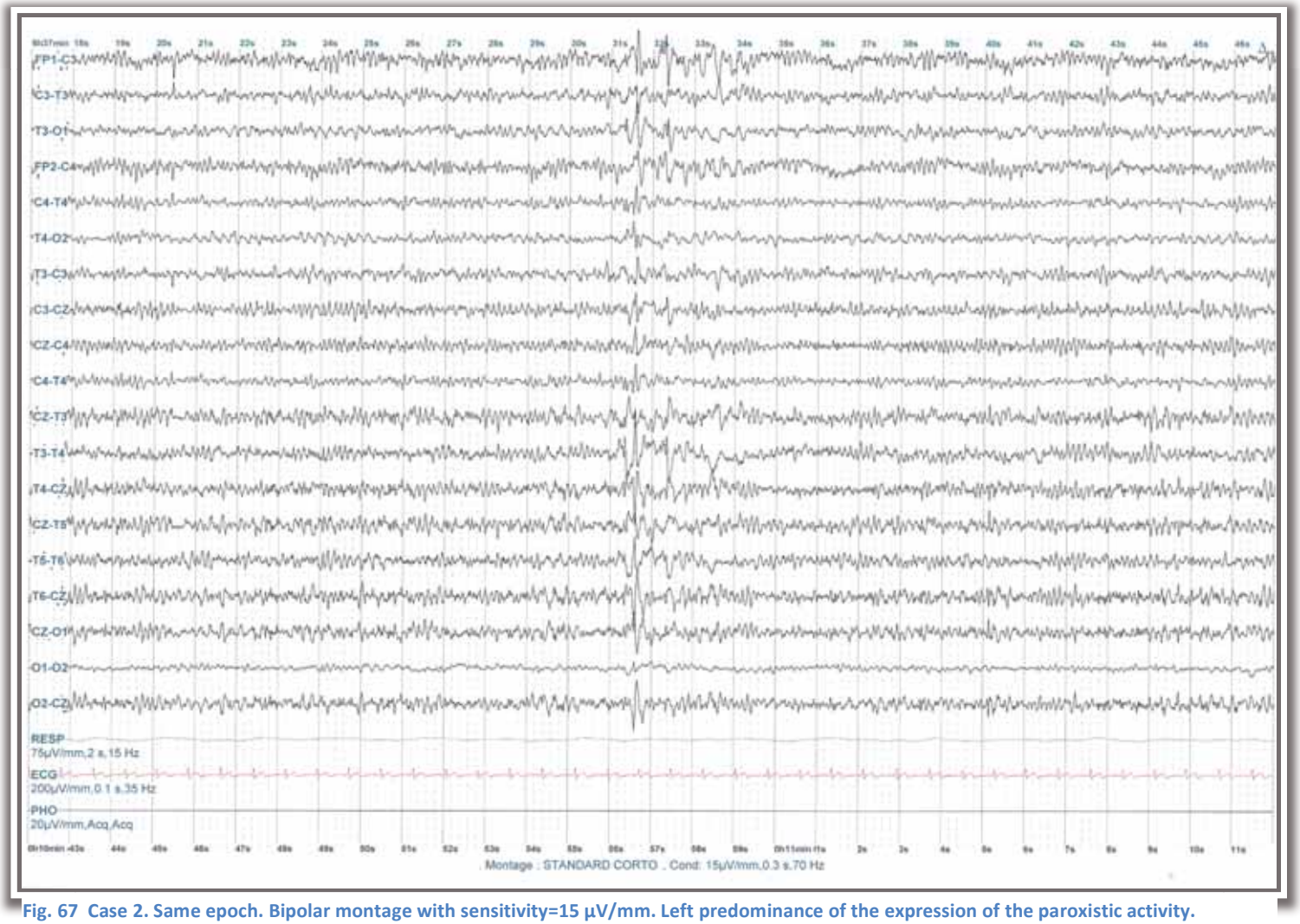


Fig. 67 Case 2. Same epoch. Bipolar montage with sensitivity=15 µV/mm. Left predominance of the expression of the paroxistic activity.

Fig.68 is the same epoch in a transversal montage.

The activity has remarkable diffusion, which makes difficult assessing the location of the focus. Given this situation it's a good idea keep on trying with other montages or EEG parameters such as sensitivity or time per page.

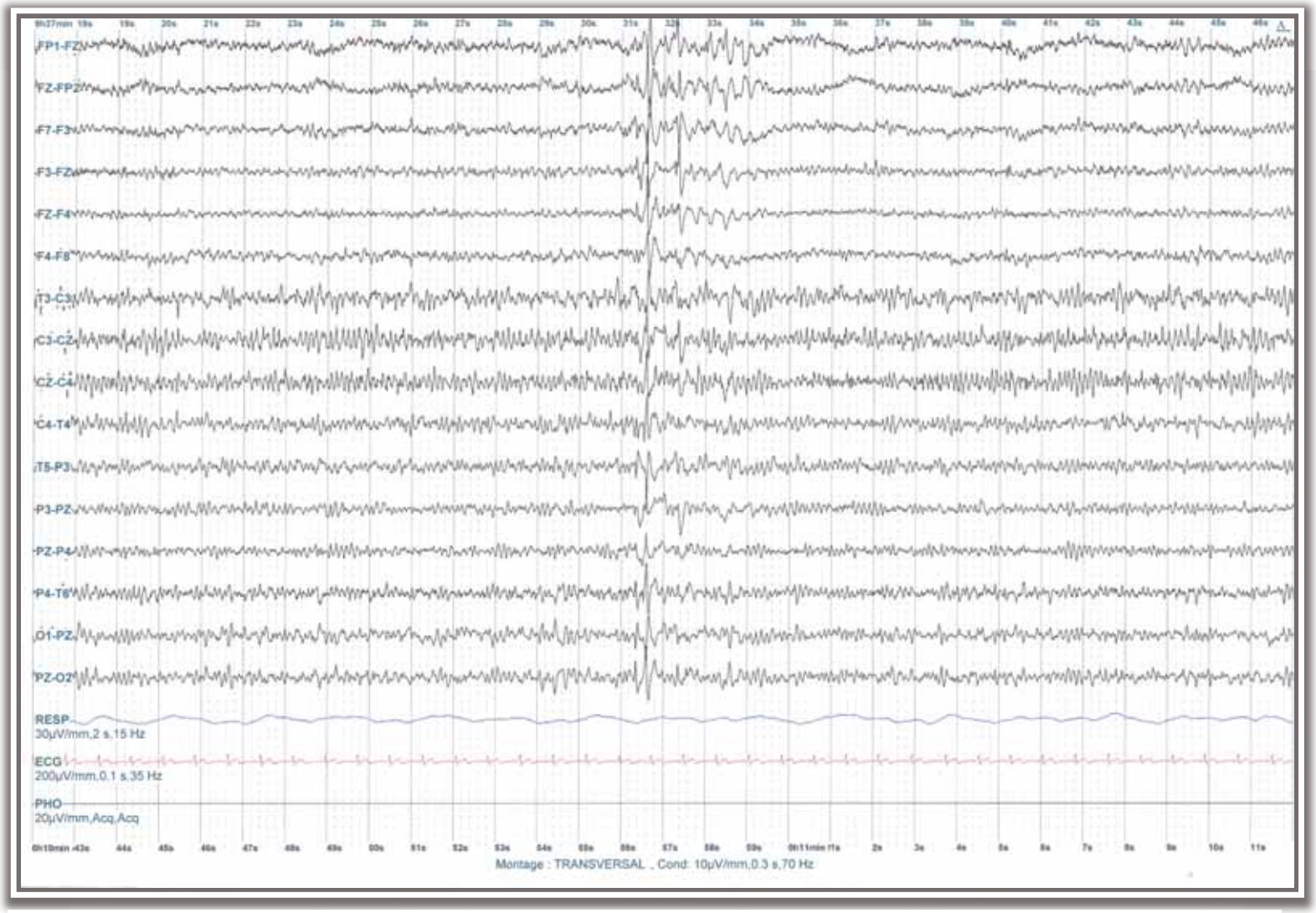


Fig. 68 Case 2. Same epoch in transversal montage.

Now we see the same epoch in referential montage with sensitivity = 15µV/mm (Fig. 69). In this picture we can see irregular slow waves with more amplitude in left front-central region (F3), with diffusion to left inferior frontal, mid-frontal and central regions and bilateral pre-frontal regions. Apart from the spiky waves we can also see some slow waves (3Hz) in frontal regions

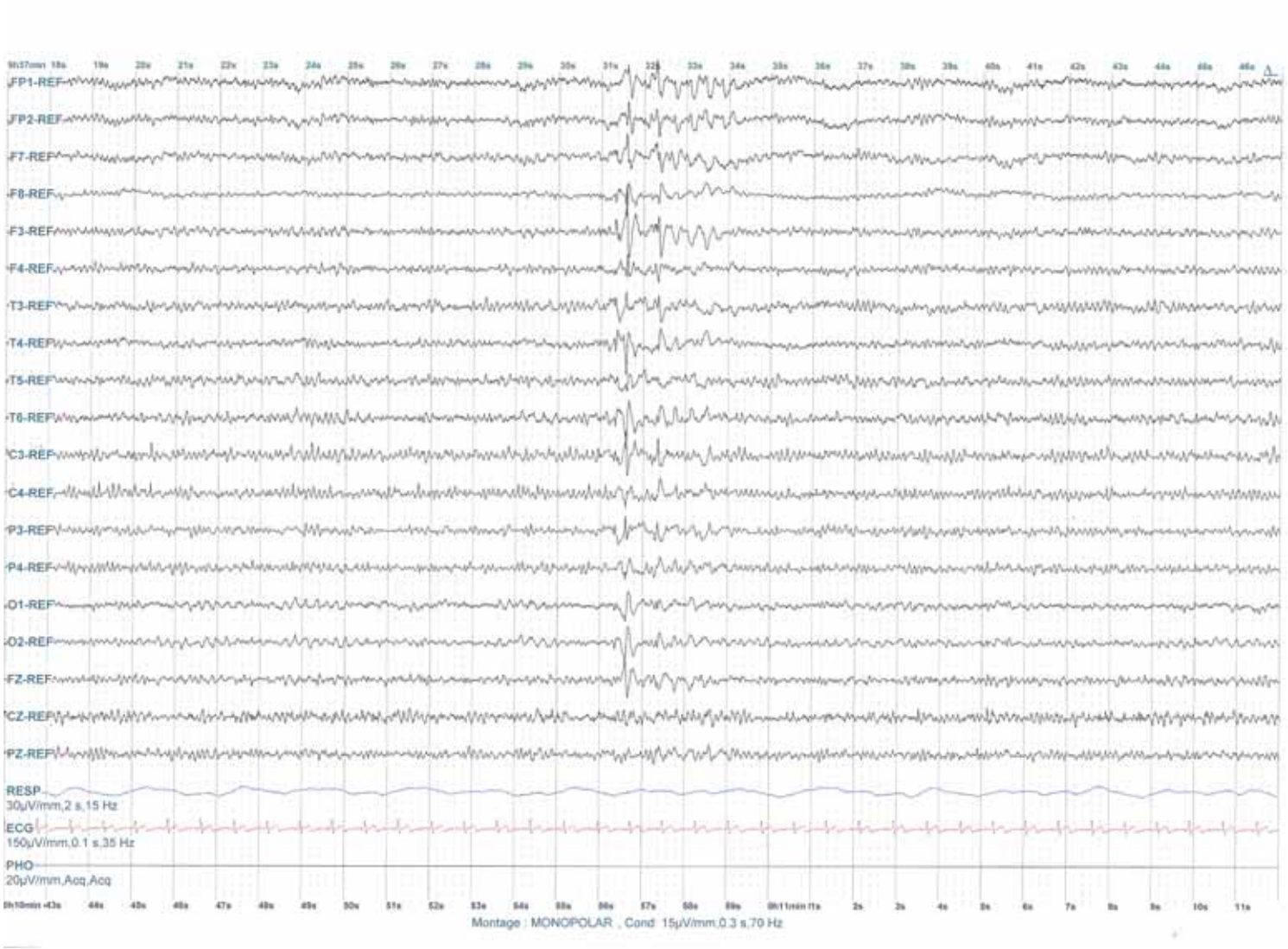


Fig. 69 Same epoch in a referential montage and sensitivity of 15 µV/mm. The referential montage helps in locating the interictal activity, with maximal expression in left fronto central region, F3, and diffusion to both prefrontal, Fp1, Fp2, F7, C4. Specular image of the IED due to the effect of referential montage in T4, T6, O1, O2.

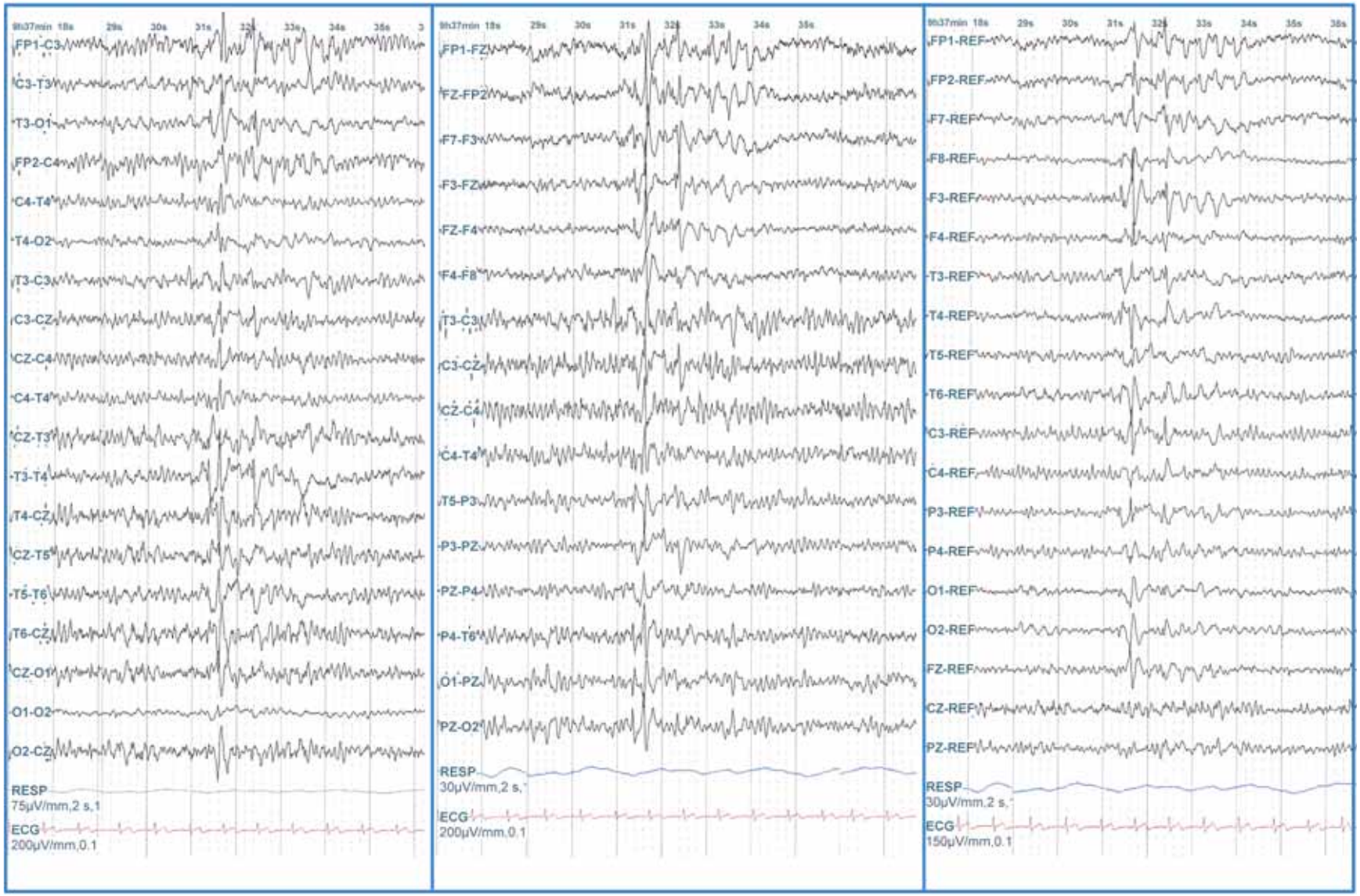


Fig. 70 Collage view of the previously shown montages: Bipolar standard, transversal and referential montages. Mzximal expression in F3, with diffusion towards both Fp1 and Fp2, F7, C3.

In the next examples we will also see the different aspect the EEG recording acquires with diverse montages. Regarding the differences in the ictal activity, Fig. 71, Standard bipolar montage shows a widespread synchronized rhythm, followed by a higher amplitude beta rhythm. We can see higher amplitude in the channels that refer to left hemisphere.

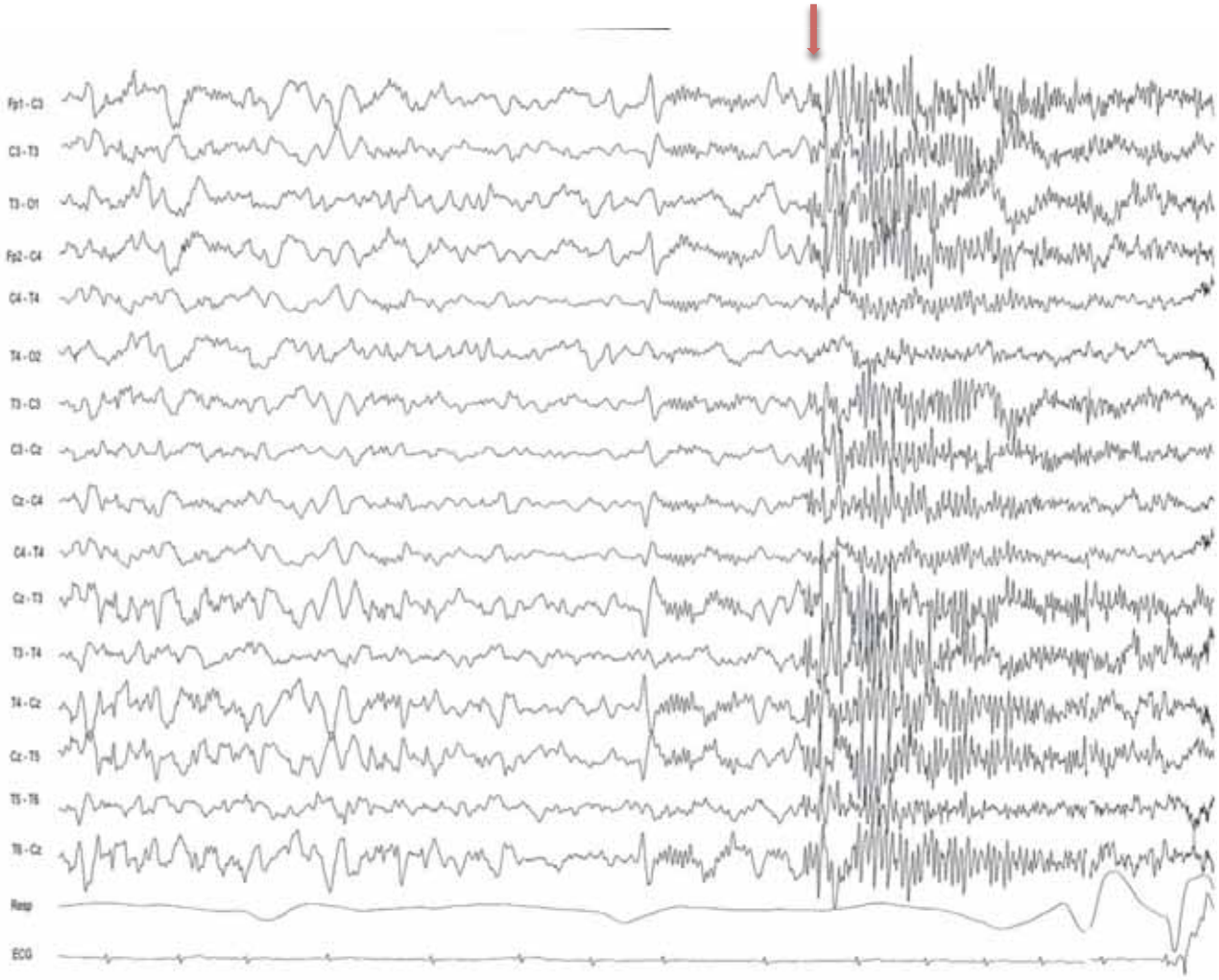


Fig. 71 Case 4. Seizure activity in a bipolar electrode setting.

Next picture (Fig. 72) shows a recorded seizure from the same patient in a referential montage.

We can appreciate higher amplitude in left frontal electrodes (Fp1, F7, F3), mainly in left front central region (F3); this higher amplitude reflects a higher electro-negativity in that cortical region.

The referential montage locates the ictal activity that was apparently diffuse with the bipolar montage.

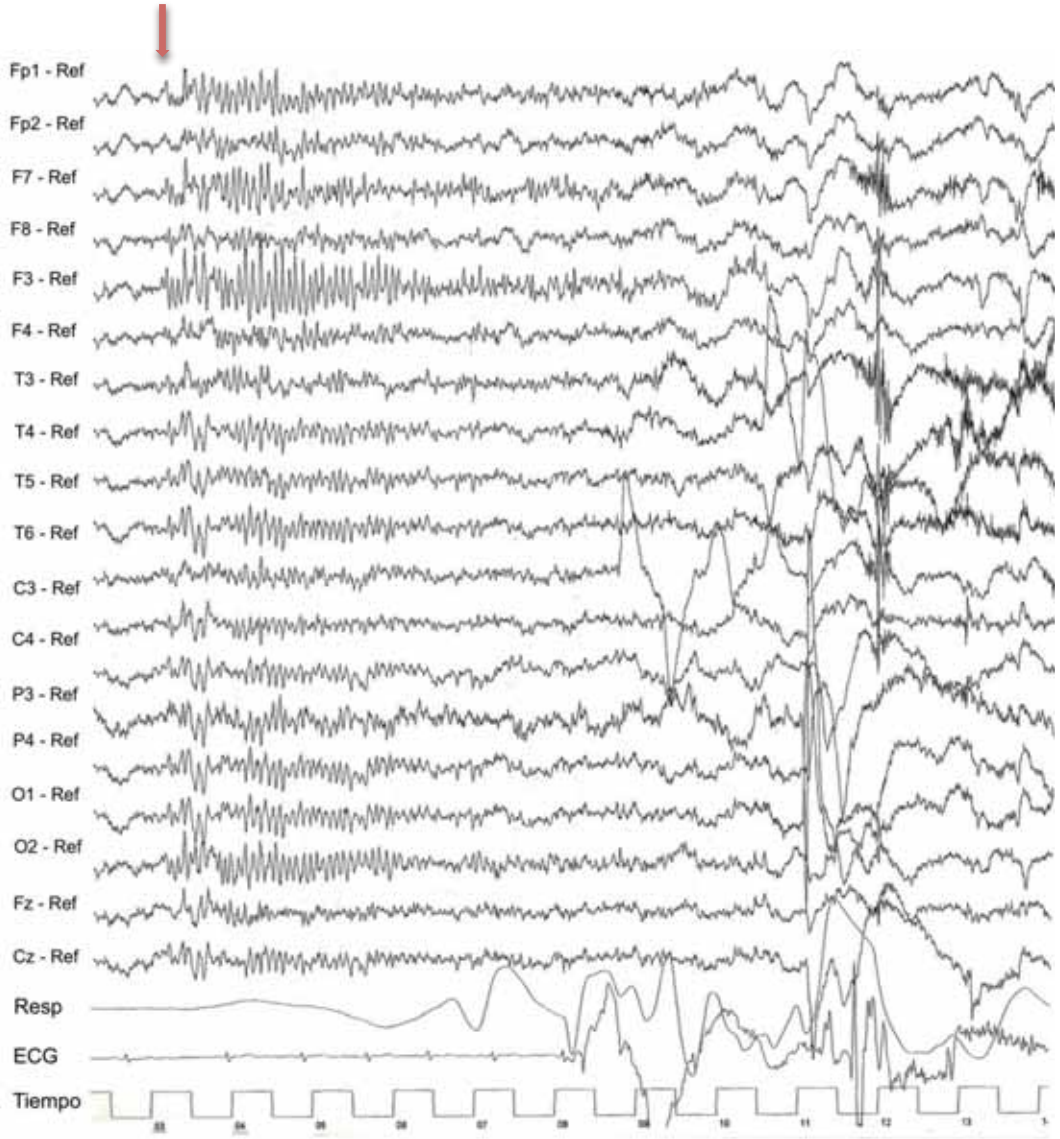


Fig. 72 Case 4. Seizure with a referential montage. Maximal expression in F3> F7, Fp1.

We can easily compare the EEG aspect within different electrode settings. In next collage we compare the same seizure in different montages to pay attention to the differences we have previously talked about.

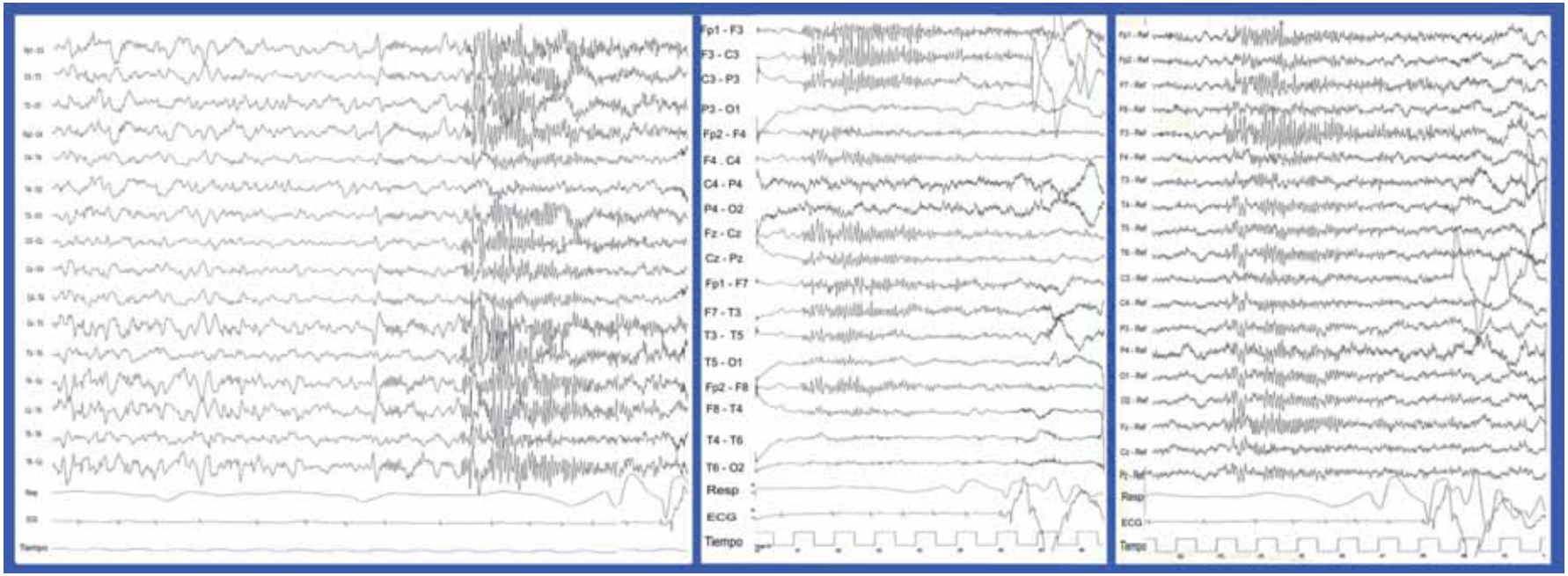


Fig. 73 Case 4. Comparison of the same seizure in three different montages: a) bipolar standard, b) bipolar longitudinal and c) referential.

In Fig. 74 we see high amplitude spikes and high amplitude diphasic sharp waves as well as irregular waves quite widespread even in a referential montage.

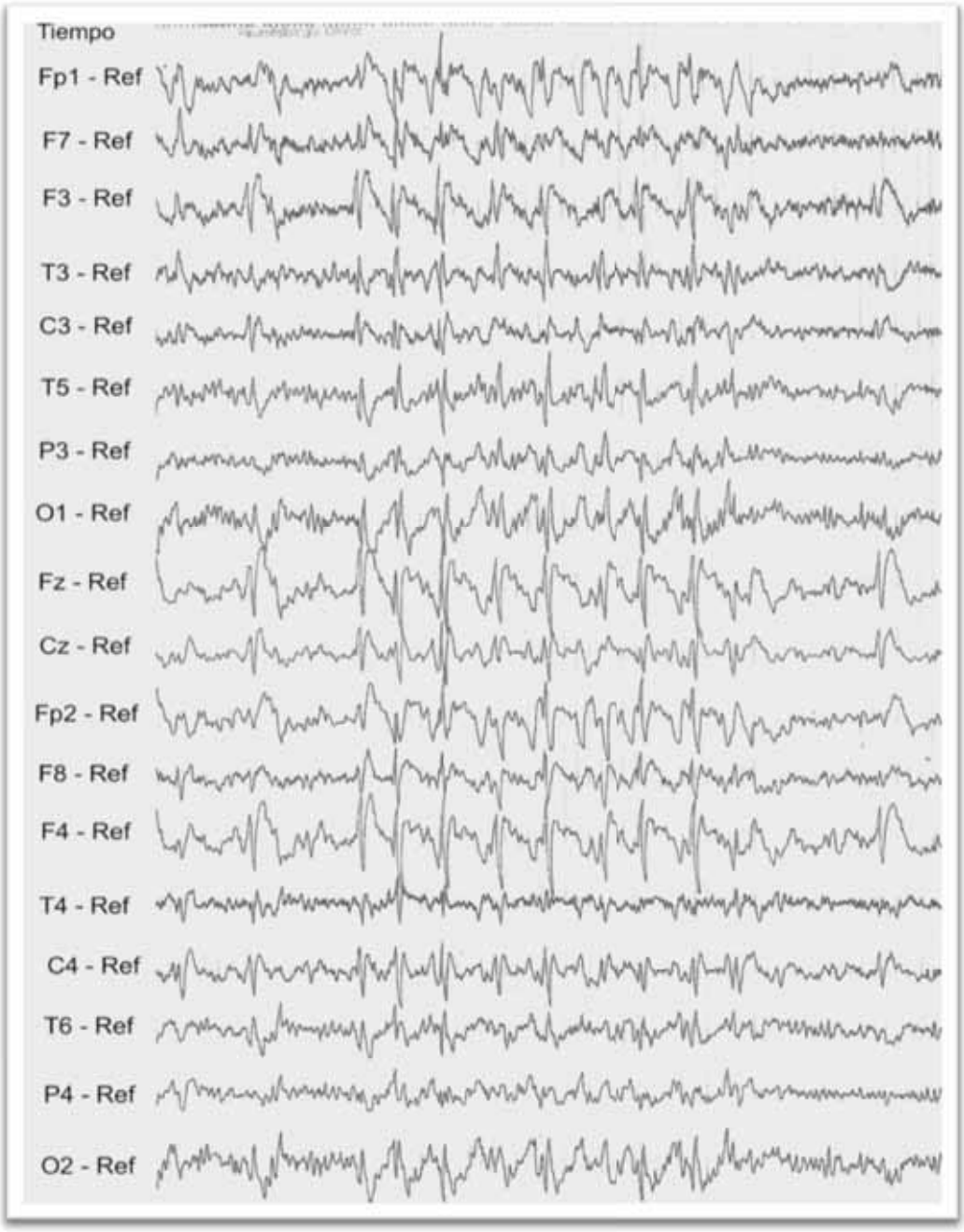


Fig. 74 Case 3. Referential montage. Great diffusion of the IED. At the end of the epoch we can appreciate a slight right predominance of the expression in F4.

When the focus is so active, with such a widespread diffusion it would be very difficult to assign an electrode responsible for the discharge. We must continue looking for an epoch where the IED is less active.

Apart from looking all the recordings before making a diagnostic impression, we will try to differentiate the morphology of the discharges and the regions where the epileptiform activity origins by changing the montage. For this purpose, one of the montages we can use is the transversal montage.

Fig. 75 shows a piece of the same recording, where focal predominantly frontal activity is shown in transverse montage. The first six channels are the most active, and hence you can tell a frontal predominance of the epileptiform activity.

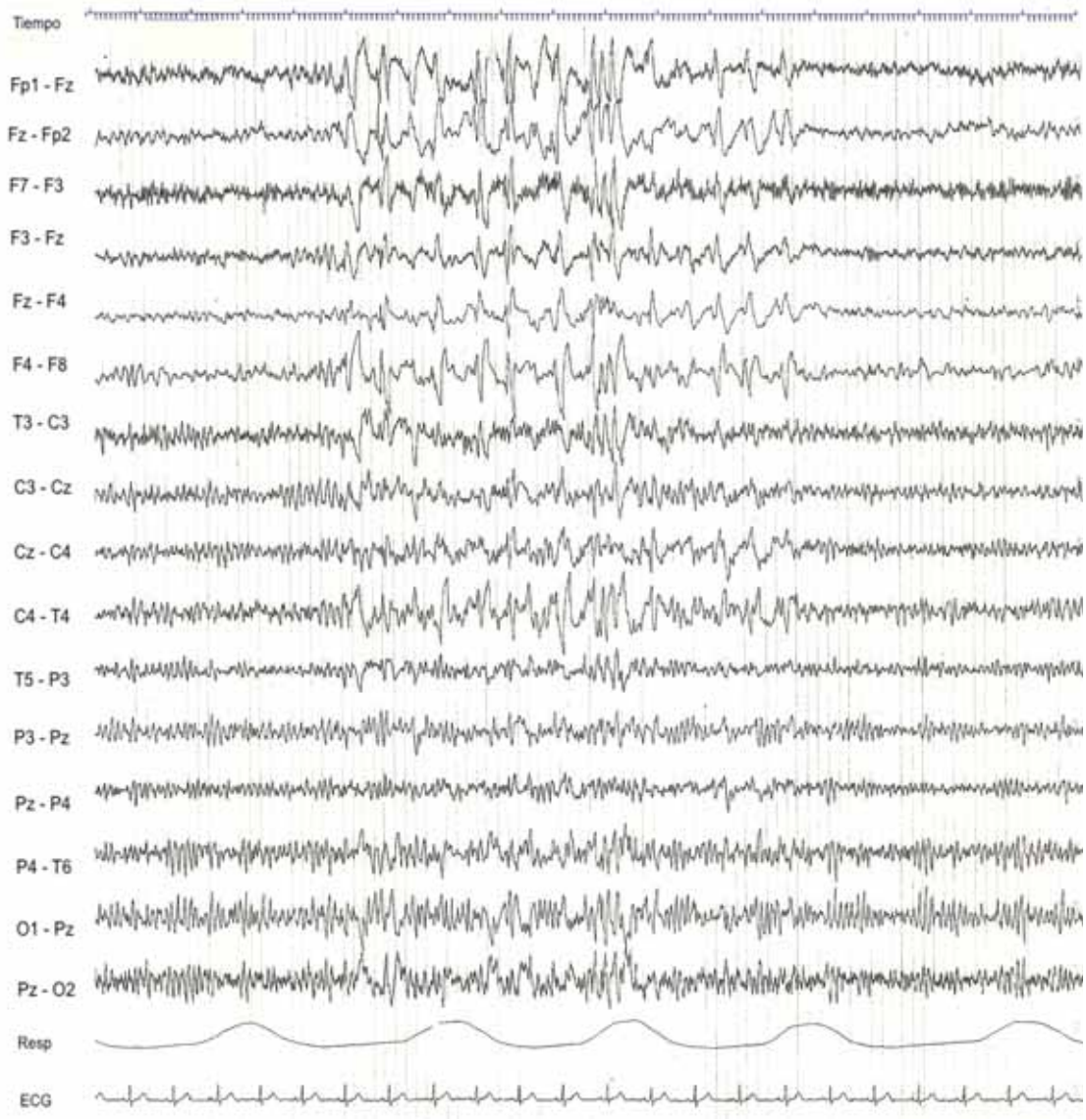


Fig. 75 Case 3. Transversal montage. We can appreciate a frontal predominance of the discharges.

Now we can use a referential montage again to try to better localize the focus in the different discharges we have. As the amplitude is so high we may need to decrease sensitivity from 10µV/mm to 15µv/mm or more if necessary.

If we look Fig. 76 (decreased sensitivity to 15µV/mm) carefully, we can in fact see a clear difference in amplitude between electrodes, with higher amplitude diphasic waves in right front-central region (F4), in spite of the diffusion of the activity that is still considerable.

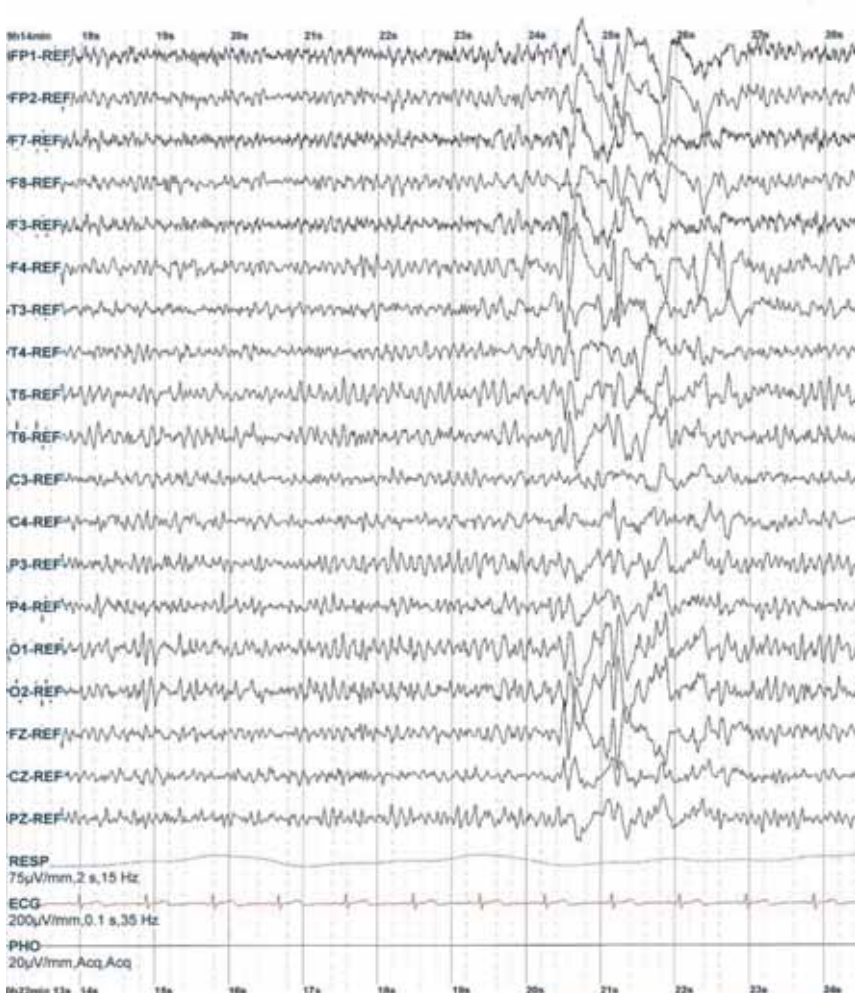


Fig. 76 Case 3. Referential montage. Higher amplitude sharp biphasic waves in right frontal regions. Maximal expression in F4>Fz, with diffusion to both Fp1 and Fp2.

In this case some seizures were registered as well:

As happened with the interictal activity, even more marked, using a bipolar montage doesn't help much in trying to assess location of seizure onset. Fig. 77 shows very high amplitude spike-slow wave with higher amplitude in front-central regions, but the diffusion of the activity and the montage (bipolar with long distances) doesn't allow differentiating not even side predominance. Then a change in activity occurs, with diffuse synchronized rhythm with beta band frequencies widespread.

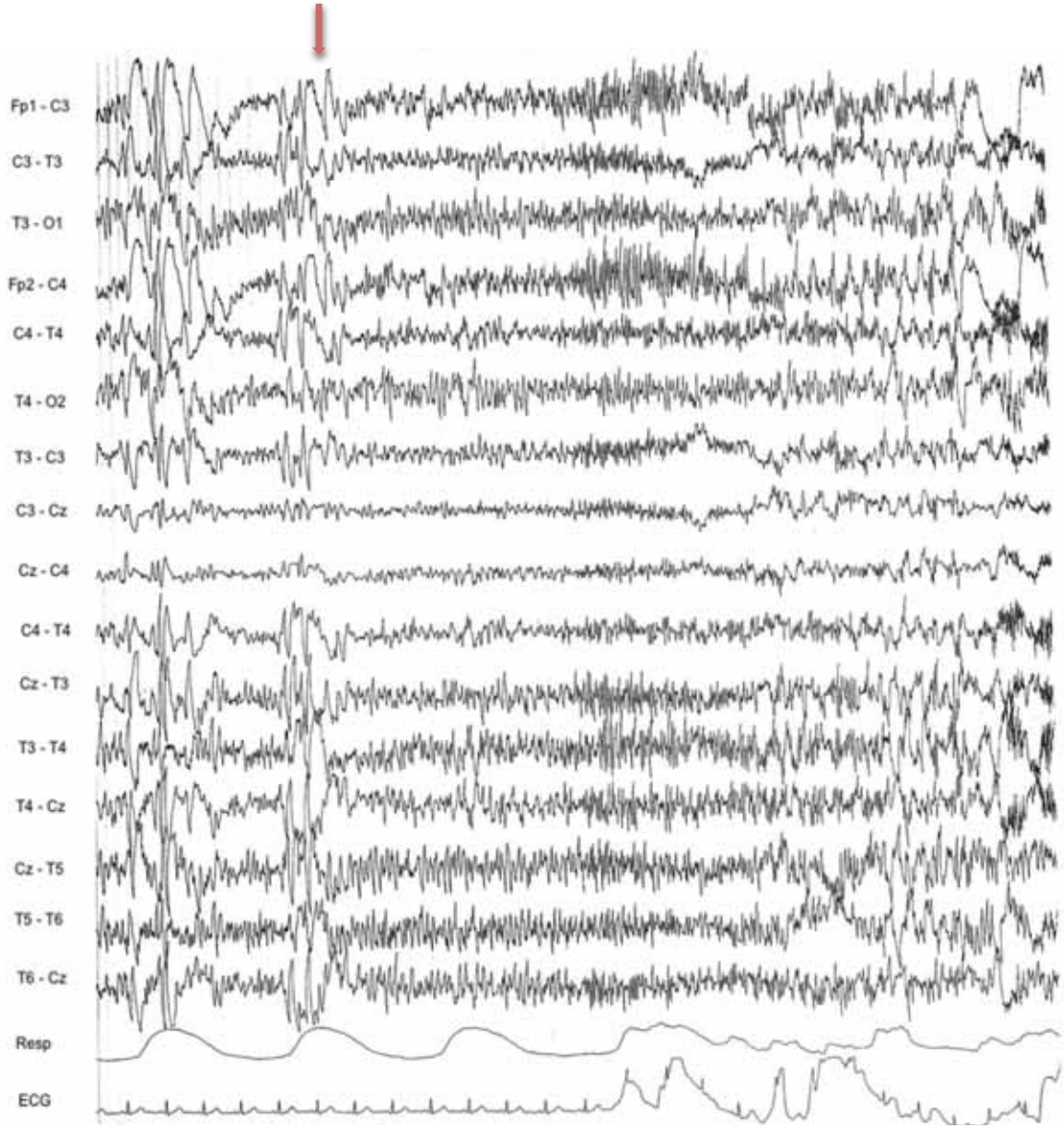


Fig. 77 Seizure seen in a "standard" bipolar montage. Synchronized rhythm with diffuse expression.

We will see now a referential recorded seizure of the same patient, to try to find out where seizure starts.

Even with decreased sensitivity, it's very difficult to see interesting details in the conventional epoch with a speed of 20s/pg. (Fig. 78).

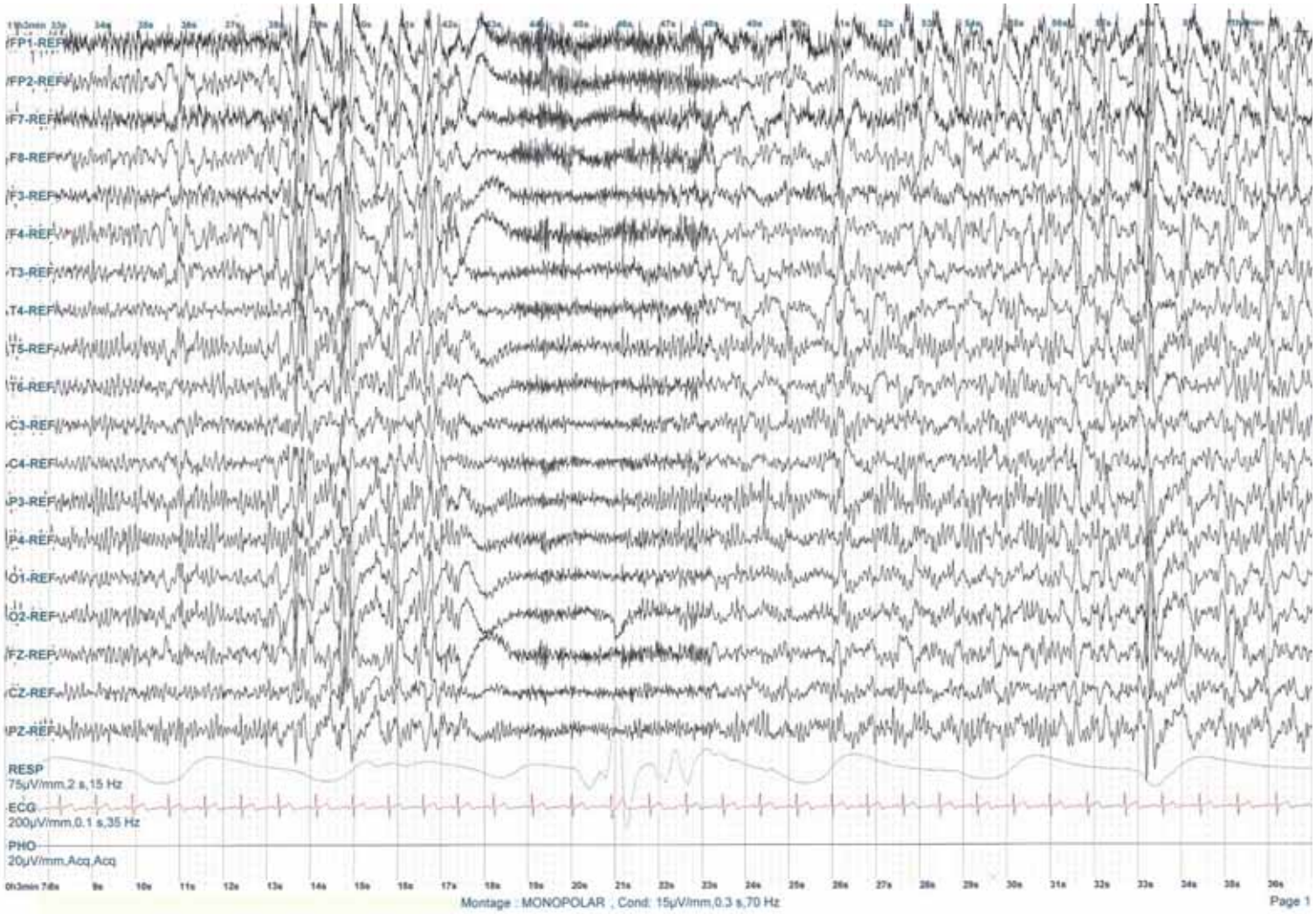


Fig. 78 Case 3. Seizure with a referential montage.20s/pg. High amplitude IED before the ictal change, with diffuse synchronized rhythm and postictal slowing and paroxistic activity afterwards.

In Fig. 79, with a referential montage, usual sensitivity (10µV/mm) and speed reference of 10s/pg., an important detail come to our view: Both in right prefrontal (Fp2) and front-central (F4) regions, just before the clear change in activity, some sharp waves are superimposed in a slow wave.

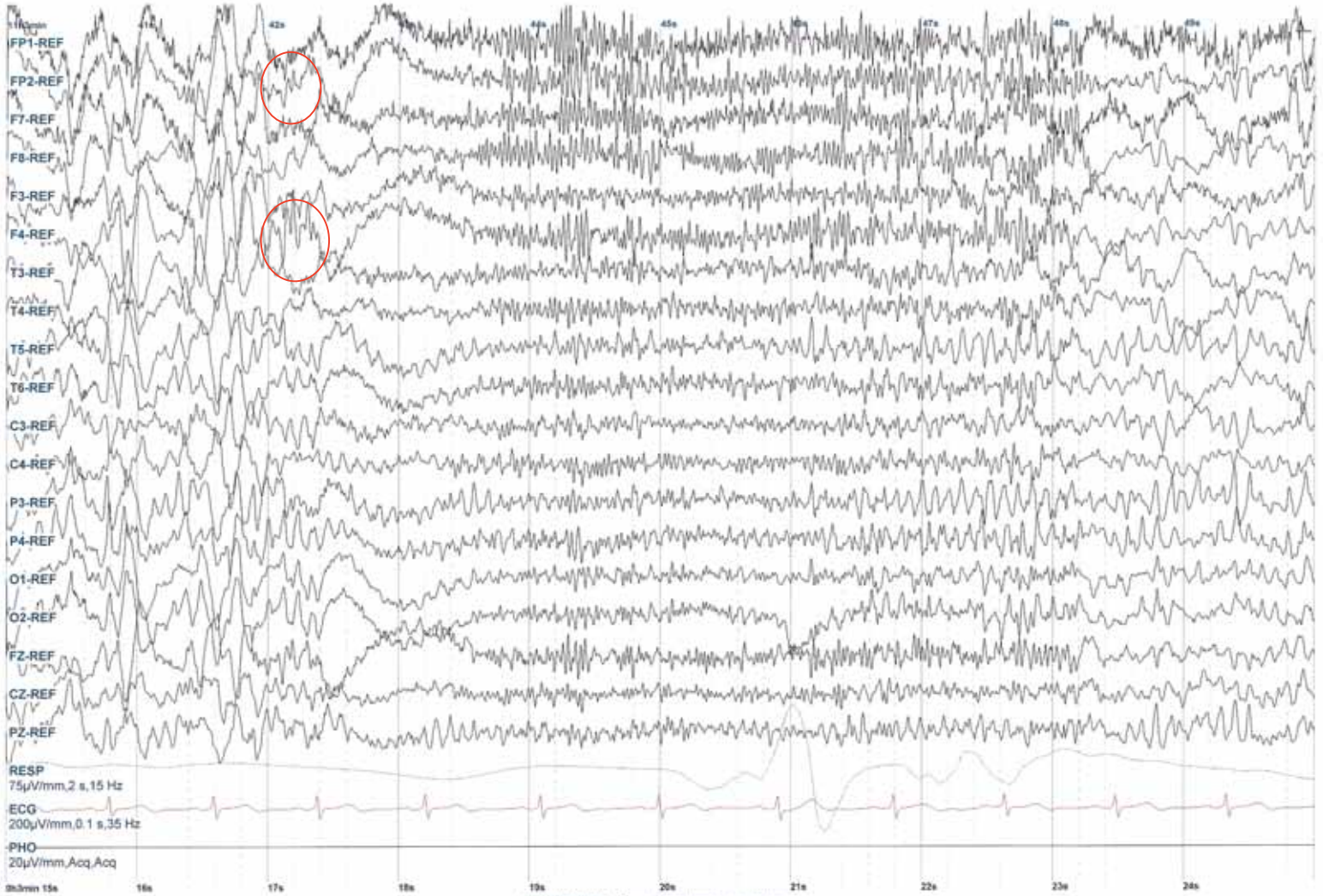


Fig. 79 Case 3. Seizure in a referential montage at 10 s/pg. Maximal expression of sharp waves in F4>Fp2 just before/at seizure onset.

We can see the same picture with 15µV/mm sensitivity to focus on this change at seizure onset.

Then an attenuation of amplitude occurs and beta frequencies appear diffusely, with higher amplitude in right frontal regions.

In many occasions we can see that epileptiform activity is a continuum in which we can see kind of some "very sort and milder" seizures than others.

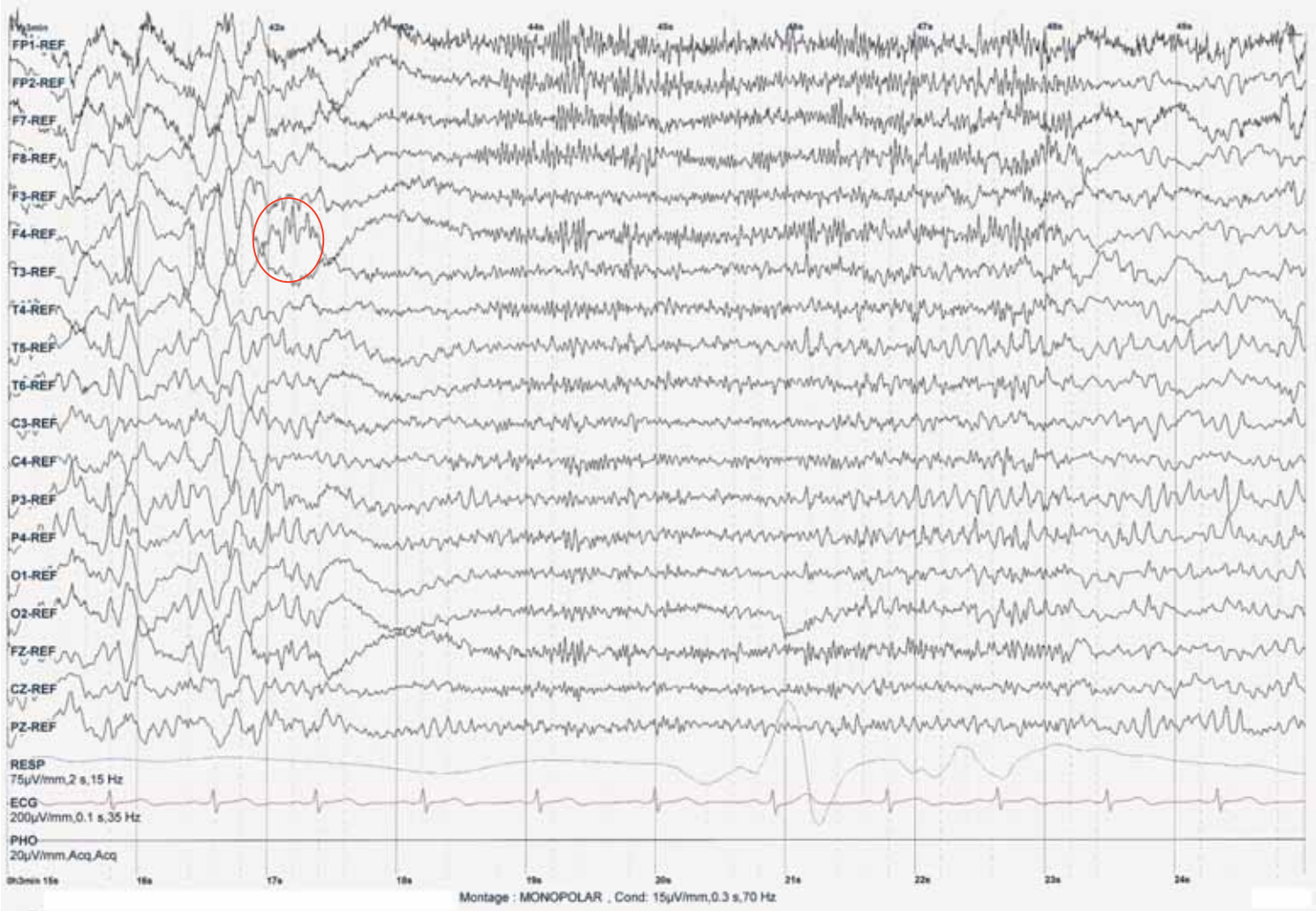


Fig. 80 Case 3. The same epoch as in pic. 10 with sensitivity decreased to 15 µV/mm. Samevelocity (10s/pg.)

In those we can identify a pattern that would remain the onset pattern of the completely developed seizures.

c) Post-ictal activity

Another useful piece of information about the recording we are working with is usually given by the post-ictal activity. Often post-ictal activity may give important clues to understand the recoding, and therefore we must stop at it and look at it carefully. You may notice a slowing in a region more than in a single electrode, but some other times a more located slowing can be observed,nreflecting the most probably region originating the seizure. Some other times, if the focus is very active, you can find immediately, after the seizures, new located discharges

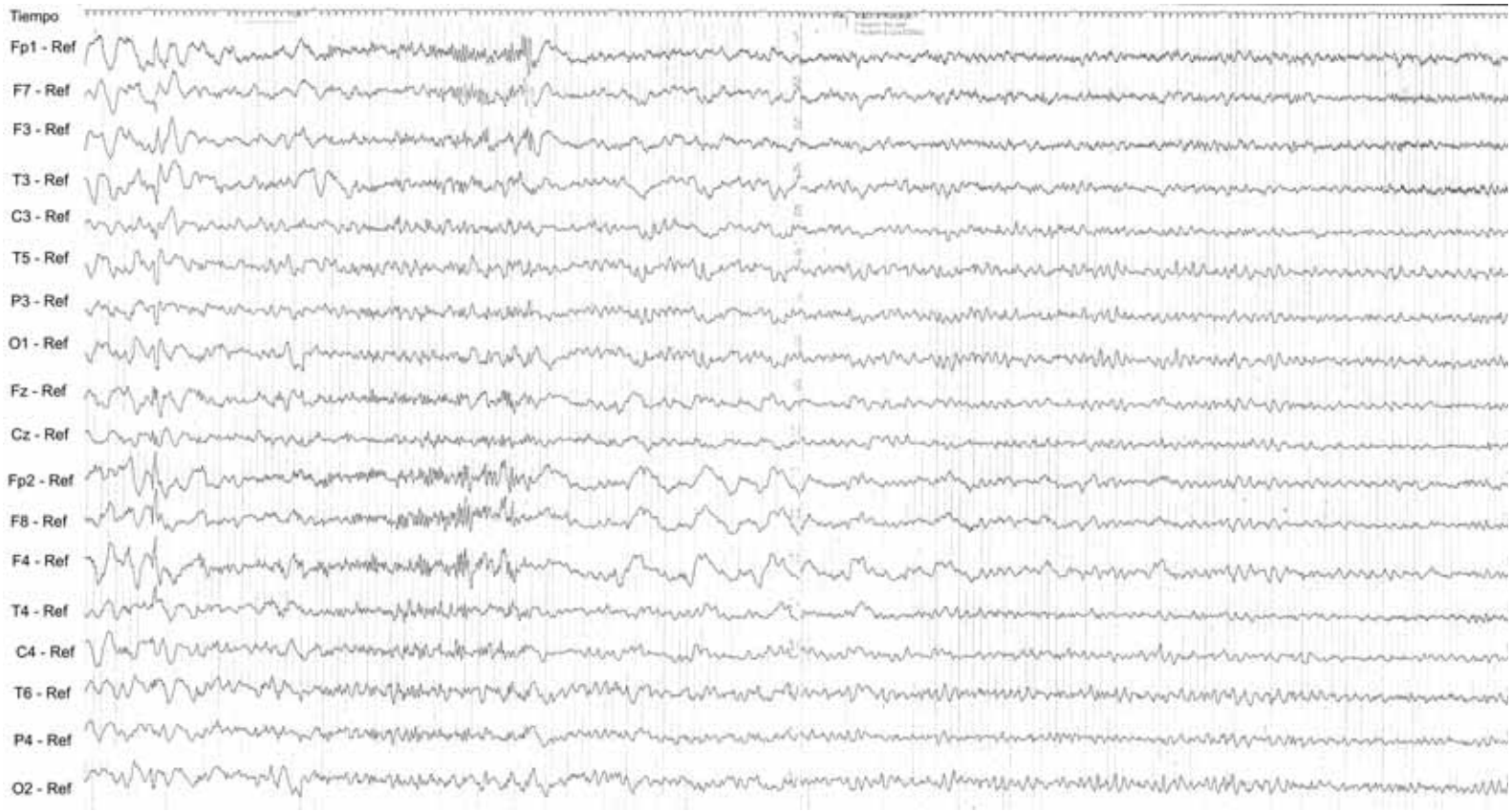


Fig. 81 Short seizure, with low amplitude synchronized rhythm, with a prominent postictal slowing in right frontal regions.

Fig.82 shows a short seizure; even thought the seizure was quite short, there is a clear slowing after it, prominent in right front-central electrode (F4).

Besides the slowing, we can see an epileptiform paroxysm in the immediate post-ictal epoch, in the same region. One more detail we can see in this seizure is that EMG artefact is prominent in left electrodes, which shows right epileptiform activity during the seizure.

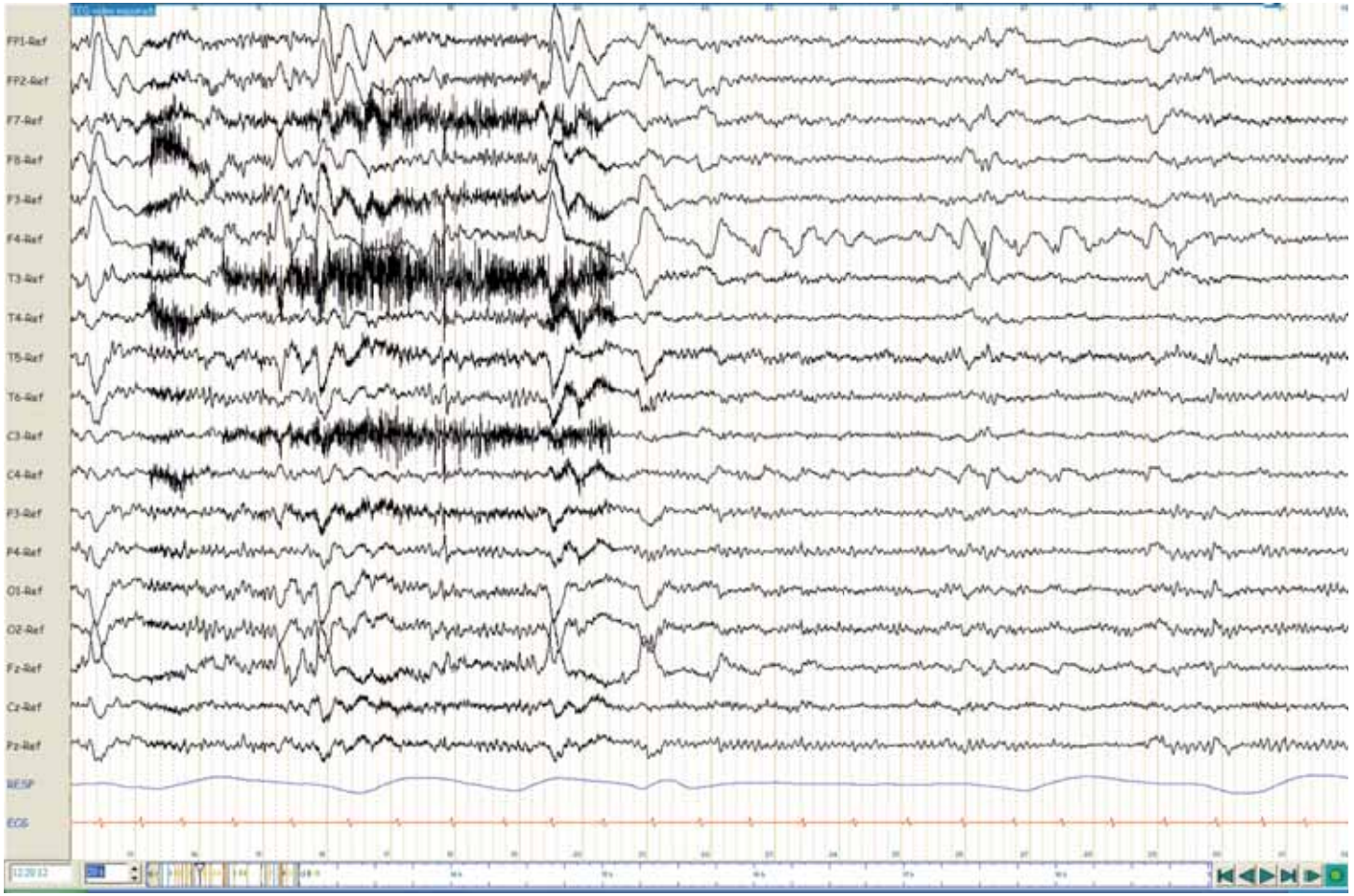


Fig. 82 Case 113. Postictal slowing and epileptiform discharge with maximal expression in right front central region (F4).

6.3 SECONDARY OBJECTIVES: STATISTICAL STUDIES

Once we know the sample and the description of the different variables, we can test statistically the hypothesis assessed.

6.3.1 Hypothesis testing: Location and morphology of seizure pattern remains the same over time for each patient.

To test this hypothesis we will focus on the cases with more than one seizure recorded. We will test whether the distribution of the variable "variability of seizure pattern" that codifies the variability of seizure pattern at onset.

The variable studied was "PatVar" that codifies de variability of seizure morphological patter at onset. Changes in amplitude and duration are permitted.

For this purpose we have analysed patients with two or more recorded seizures, so that its variability can be assessed.

With this condition we have 41 cases, divided into two possible values, "0" if the morphological pattern remains the same over time, and "1", if the morphological pattern changes over time in different seizures for the same case.

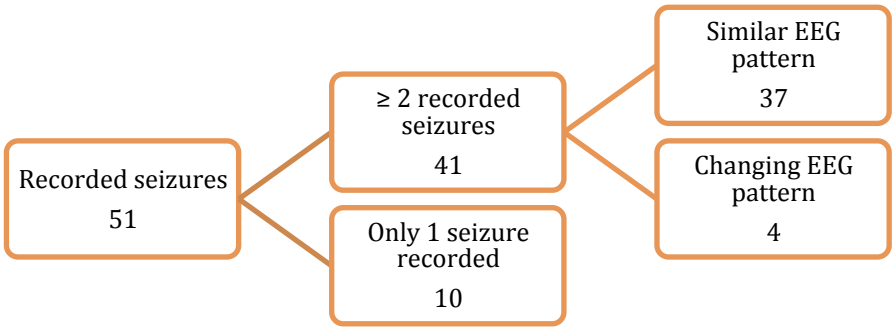


Fig. 83 Variability of seizure pattern.

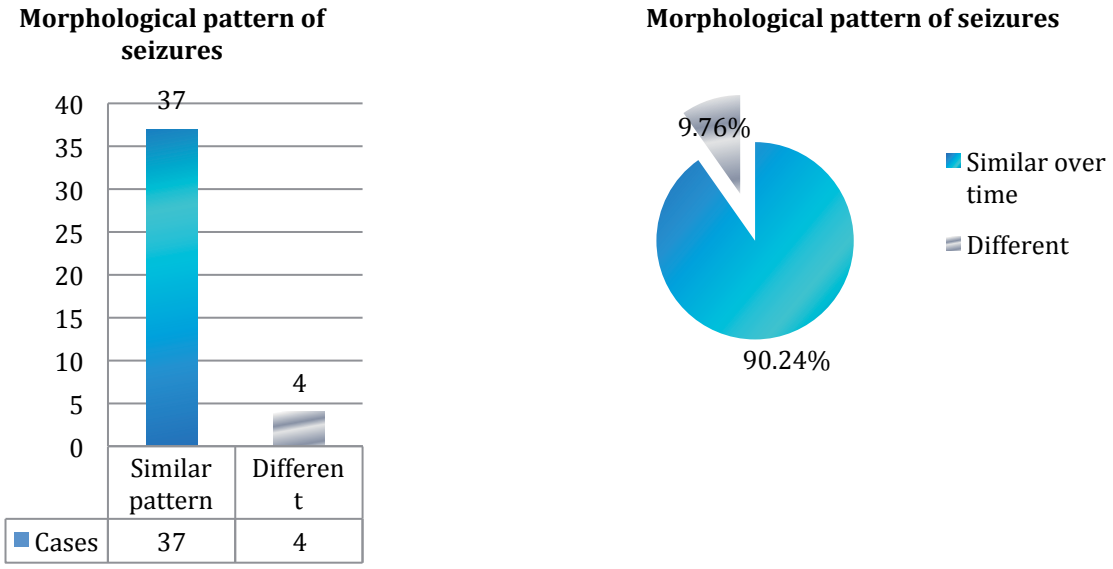


Fig. 84 Diagrams for the distribution of the variability of seizure pattern on the sample.

Frequency table shows de distribution of the variable “PatVar”

Value	Absolute	Relative
0	37	0.9024
1	4	0.0976

Table 3 Distribution of the variable.

Now we test the hypothesis of the proportion of cases in each category. The test is related to the proportion (theta) on a binomial distribution, expected to be of 0,5 at random (H0). The proportion of the studied value (PatVar=0) in the sample is 0,9024, in a sample sized 41. The confident interval of 95% for the proportion is [0.77; 0.97]. Moreover, the contrast H0: p=0,5 versus H1: p≠ 0,5 concluded a p-value= 1.16174 * 10-7.

We can conclude that in our sample the distribution of the variable is different from what would be expected by random (50%), and therefore **location and morphology of seizure pattern remains the same over time for each patient**, with statistical significance.

6.3.2 Hypothesis testing: There is a significant relation between location of seizure onset and location of interictal activity in the whole population.

To test this hypothesis, all patients with registered seizures were studied and classified according to the electrode assessed as the one responsible for the seizure onset when possible, and if not by the hemisphere origin (left versus right) or a not localisable origin.

This is the cross-tab for the statistic test, between the variables: "location of interictal activity" and "Location of seizure onset" for those patients with recorded seizures. 51 patients had recorded seizures. In 8 of them the location of seizure onset could not be assigned to neither one electrode nor even a hemisphere origin. In those cases the location of the Interictal activity was very diffuse, located in several electrodes so we decided to exclude them for the analysis given the fact that it would not contribute to clarify any relation between the variables in study. Excluding the "non-located" seizures we have 43 patients with recorded seizures:

		Location of the interictal activity									
		Fp1	Fp2	F3	F4	Fz	F7	F8	Left	Right	Total per
Location of seizure onset	Fp1	5 11.63%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	5 11.63%
	Fp2	0 0.00%	2 4.65%	0 0.00%	1 2.33%	0 0.00%	0 0.00%	0 0.00%	1 2.33%	0 0.00%	4 9.30%
	F3	0 0.00%	0 0.00%	5 11.63%	0 0.00%	0 0.00%	1 2.33%	0 0.00%	0 0.00%	0 0.00%	6 13.95%
	F4	0 0.00%	0 0.00%	0 0.00%	4 9.30%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	4 9.30%
	Fz	0 0.00%	0 0.00%	0 0.00%	0 0.00%	1 2.33%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	1 2.33%
	F7	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	8 18.60%	0 0.00%	0 0.00%	0 0.00%	8 18.60%
	F8	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	5 11.63%	0 0.00%	0 0.00%	5 11.63%
	Left unspecific	0 0.00%	0 0.00%	2 4.65%	1 2.33%	0 0.00%	1 2.33%	0 0.00%	1 2.33%	0 0.00%	5 11.63%
	Right unspecific	0 0.00%	0 0.00%	0 0.00%	2 4.65%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	3 6.98%	5 11.63%
	Total per column	5 11.63%	2 4.65%	7 16.28%	8 18.60%	1 2.33%	10 23.26%	5 11.63%	2 4.65%	3 6.98%	43 100.00%

Table 4 Crosstab of Location of the interictal activity and Loc. of seizure onset (patients with recorded seizures).

If we analyse this data regarding the location of seizure onset we have the following table:

Location of seizure onset	Location of the Interictal activity							
		Fp1	Fp2	F3	F4	Fz	F7	F8
	Fp1	5 100.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%
	Fp2	0 0.00%	2 50.00%	0 0.00%	1 25.00%	0 0.00%	0 0.00%	0 0.00%
	F3	0 0.00%	0 0.00%	5 83.33%	0 0.00%	0 0.00%	1 16.67%	0 0.00%
	F4	0 0.00%	0 0.00%	0 0.00%	4 100.00%	0 0.00%	0 0.00%	0 0.00%
	Fz	0 0.00%	0 0.00%	0 0.00%	0 0.00%	1 100.00%	0 0.00%	0 0.00%
	F7	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	8 100.00%	0 0.00%
	F8	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	0 0.00%	5 100.00%

Table 4: Crosstab with well located epileptiform activity, only including specific cases.

We can see as the diagonal of the table has the majority of the data. That means that seizures that origins on an electrode usually has the Interictal activity located on the same electrode.

Mosaic graphical view of this data shows the same

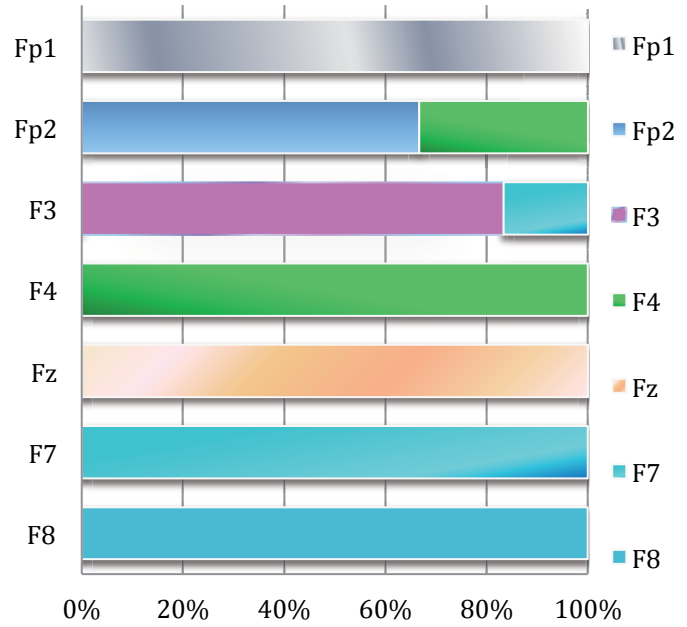


Fig. 85 Mosaic graphic: At left seizure location of seizure onset, excluding unspecific cases. The colour refers to the location of the Interictal activity.

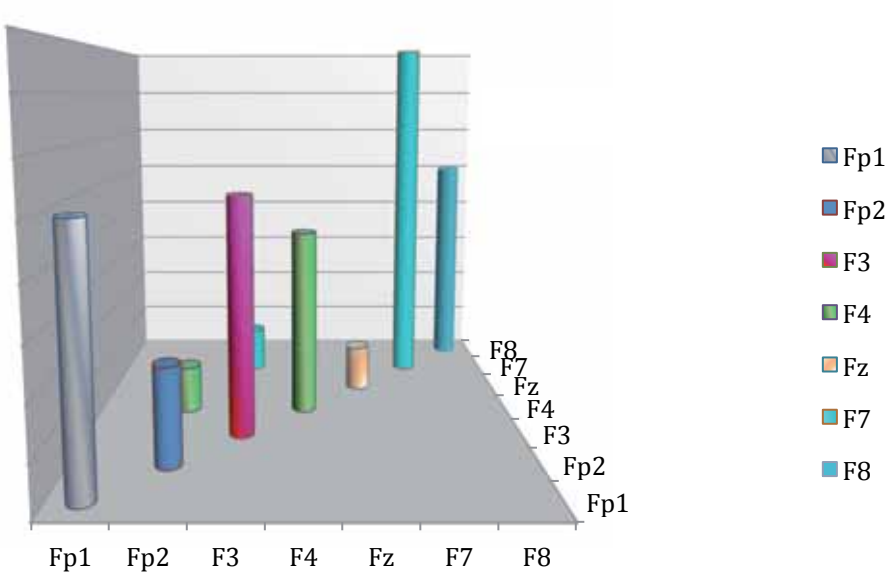


Fig. 86Graphic of the association between location of seizure onset and location of the Interictal activity for the well localized seizures.

A Chi2 test has been performed to see whether there exist a ration between the location of seizures and location of IED. The null hypothesis (H0) means that both variables are independent, and the alternative one (H1) means a relation between them.

Chi-square	Gl	p-Value
237.680	64	0.0000

Table 5 Test.

Regarding the test there exist a relation between the variables location of seizure onset and location of Interictal activity. To see the nature of this relationship we see a correlation coefficient, in this case we have use Pearson's R.

Statistic	Value	p-Value	Gl
Pearson's R	0.6666	0.0000	41

Table 6 Correlation coefficient.

This support a positive correlation between the variable, already intuited by the crosstab and the mosaic graphic: **there exists a significant relation between the location of the seizure onset with the location of the Interictal activity**[17].

Out from this data we can see the good relation already commented, meaning that when the seizure onset was clear, most of the cases had the Interictal activity also located on that electrode. Nevertheless when the seizure could not be given a responsible electrode to its onset was codified in left hemisphere, right hemisphere of totally unspecified. In those cases most of the foci where located in both front-central regions[18].

This could mean that foci of front-central regions arouse from deeper regions or have greater diffusions, which makes both the location of the foci and the location of the seizure onset more complicated.

When the focal activity had an unspecified location, the seizure did not help in locating the most active electrode neither.

[17] All the test with a p- Value of 0,0000.

[18] Only one case codified at seizure onset as unspecific had de focous located on inferior-frontal (F7) (an electrode different from “frontocentral” or “Unspecific”).

6.3.3 Analysis of a potential relation between location of seizure onset and the morphological aspect of seizure onset

We have studied the morphological characteristic at seizure onset regarding the location of the seizure onset.

	Synchronized rhythm without other specification	Low amplitude synchronized rhythm	Attenuation	Spike/sharp wave within a slow wave	Total per row
Fp1	5 100.00%	0 20.00%	0 0.00%	0 0.00%	5 100.00%
Fp2	2 75.00%	1 25.00%	0 0.00%	0 0.00%	3 100.00%
F3	2 33.33%	2 33.33%	2 33.33%	0 0.00%	6 100.00%
F4	2 50.00%	1 25.00%	0 0.00%	1 25.00%	4 100.00%
F7	5 62.5%	2 25%	0 0.00%	1 12.50%	8 100.00%
F8	2 50.00%	1 25.00%	1 25.00%	0 0.00%	4 100.00%
Fz	1 100.00%	0 0.00%	0 0.00%	0 0.00%	1 100.00%
Left unspecific	0 0.00%	2 40.00%	2 40.00%	1 20.00%	5 100.00%
Right unspecific	0 0.00%	2 40.00%	2 40.00%	1 20.00%	5 100.00%
unspecific	1 12.50%	1 12.50%	3 37.50%	3 37.50%	8 100.00%

Table 7 Distribution of morphological pattern at seizure onset by electrodes.

51 seizures were studied at onset. The most frequent characteristic at onset was a synchronized rhythm without other specification, and low amplitude synchronized rhythm was the second most frequent morphologic pattern at onset.

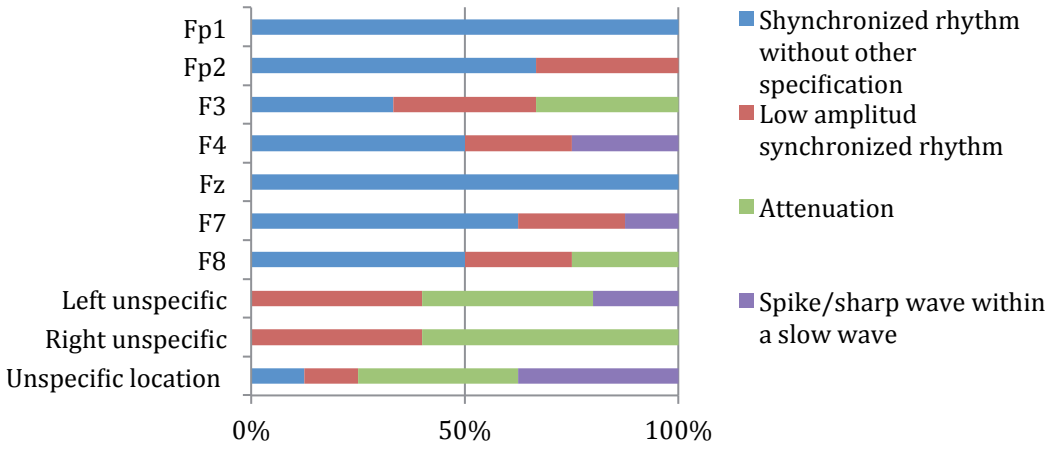


Fig. 87 Bar diagram for location of seizure onset regarding characteristic at onset.

We did not find any difference between location of seizure onset and morphology at onset:

Test	Statistic	Gl	p-Value
Chi-square	25.260	27	0.5599

Table 8 Test.

To measure the grade of association the statistics used are lambda and the contingency coefficient. Those are the following:

Statistic	Symmetrical	Row dependent	Colum dependent
Lambda	0.1286	0.0952	0.1786

	Value
Contingency coefficient	0.5793

Table 9 Contingency coefficient.

We can see as the independence test used, Chi square, and the association test lambda and contingence coefficient do not have significant values to support that there exist a relation between the variables with a 95% of confidence. **We do not find a statistical correlation between the two variables.**

Graphic by grouping the location at seizure onset by homologue regions:

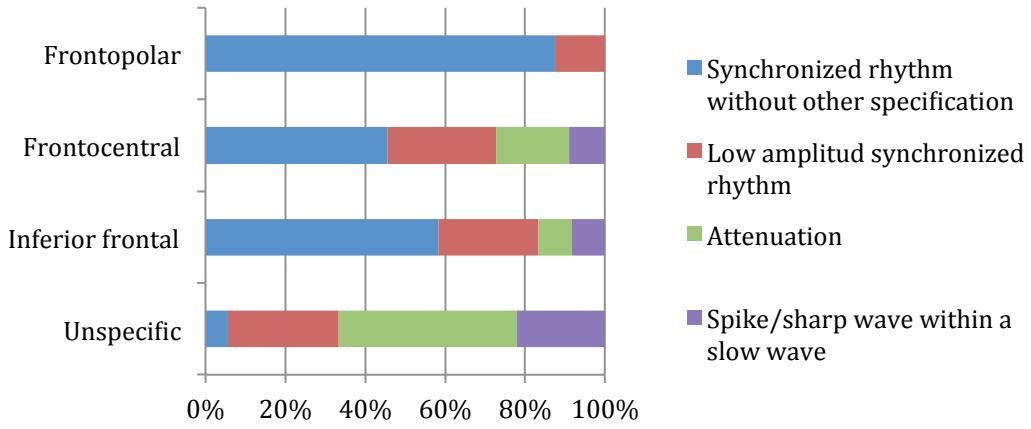


Fig. 88 Bar diagram for location of seizure onset regarding characteristic at onset, grouped by homologue regions.

Test	Statistic	Gl	p-Value
Chi-square	9.748	9	0.3713

Table 10 Test.

As previously seen without grouping by homologue regions, there is no relation between the location of seizure onset and the morphologic characteristics at seizure onset.

In spite of the lack of association we can see that the seizures arising from prefrontal electrodes did not show any seizure with attenuation at onset, and at the same time, this pattern was the most commonly seen in the seizures wit “unspecific” location of onset.

6.3.4 Analysis of the frequencies during seizures

a) There is a progressive slowing of the observed frequencies from the start of the seizure.

We have studied the free three observed frequencies from seizure onset, from a visual point of view, and codified them in three variables. The subsequent analyses of the values are as follow:

Mean frequencies:

	Mean frequency	Standard Error	Alfa	Confidence interval (CI 95%)
1st Frequency	15.4510	1.3004	0.05	(12.8391-18.0629)
2nd Frequency	9.5935	1.0119	0.05	(7.5610-11.6260)
3th Frequency	7.1057	0.9898	0.05	(5.1177-9.0938)

Table 11 Mean of the first three frequencies observed sequentially during the seizure.

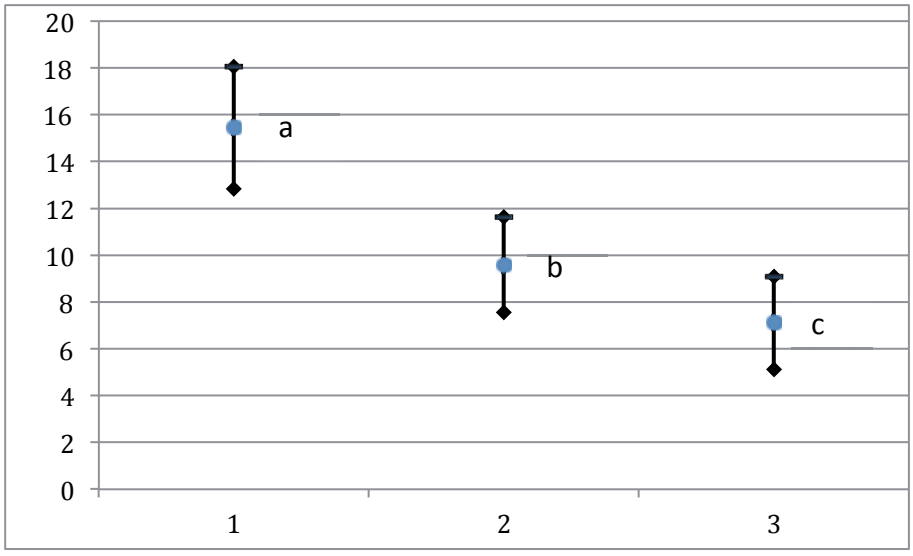


Fig. 89 Mean values for the three first frequencies during the seizures, mean and CI 95%. Means with different letters are significantly different with α = 0.05.

We can see that the differences between these mean values are significantly different[19] in the sample from a statistical point of view.

Effect	Freq	Freq	Estimate	Std. Error	df	Value t	Pr> |t|	(CI 95%)
Frequencies	1	2	5.8575	0.9996	50	5.86	<.0001	(3.8498-7.8652)
Frequencies	1	3	8.3453	1.2884	50	6.48	<.0001	(5.7574-9.331)
Frequencies	2	3	2.4878	1.1894	50	2.09	0.0416	(0.09880-.8768)

Table 12 Differences of the mean values.

We performed a chi^2 test to see if these differences are statistically significant, what is confirmed with the test, see statistic appendix for detailed data[20]. There exists progressive slowing of frequencies, with a difference of 5Hz between the first observed frequency and the second one, and of 2 Hz between the second and third observed frequency.

b) *Analysis of the frequency at seizure onset*

The seizures usually start with beta frequency. We can see the distribution of the frequency at seizure onset in the sample:

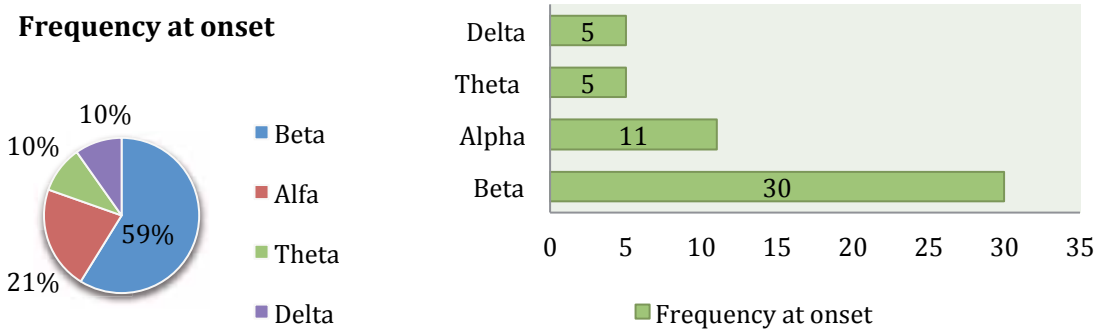


Fig. 90.1, 85.2 Frequencies at seizure onset.

[19]With a 99% of confidence in the first two cases and with a 95 % of confidence in the third one.

	Fp1	Fp2	Fz	F3	F4	F7	F8	Total
1Beta	2	0	0	6	1	3	2	14
	14.29%	0.00	0.00	42.86%	7.14%	21.43%	14.29%	
2Alfa	2	2	0	0	1	4	1	10
	20.00%	20.00	0.00	0.00%	10.00%	40.00%	10.00%	
3Theta	0	1	1	0	1	0	1	4
	0.00%	25.00	25.00	0.00%	25.00%	0.00%	25.00%	
4Delta	1	0	0	0	1	1	1	4
	25.00%	0.00	0.00	0.00%	25.00%	25.00%	25.00%	
Total per	5	3	1	6	4	8	5	32
Column	15.63%	9.38	3.13	18.75%	12.50%	25.00%	15.63%	100.00

Table 13 Distribution of frequencies at seizure onset by electrodes.

We can group the cases by homologue regions, having this table as a result:

	Fp1, Fp2	F3, F4, Fz	F7, F8	Total per row
1Beta	2	7	5	14
	14.29%	50.00%	35.71%	
2Alfa	4	1	5	10
	40.00%	10.00%	50.00%	
3Theta	1	2	1	4
	25.00%	50.00%	25.00%	
4Delta	1	1	2	4
	25.00%	25.00%	50.00%	
Total per column	8	11	13	32
	25.00%	34.38%	40.63%	100.00%

Table 14 Distribution of frequencies at seizure onset by homologue regions.

We have done a third analysis of the date, regarding hemisphere side. This is the table of the results:

	Right	Left	Total per row
1Beta	6	15	21
	14.63%	36.59%	
2Alfa	5	6	11
	12.20%	14.63%	
3Theta	3	1	4
	7.32%	2.44%	
4Delta	3	2	5
	7.32%	4.88%	
Total per column	17	24	41
	41.46%	58.54%	

Table 15 Distribution of frequencies at seizure onset by hemisphere.

Analysis of this data shows a relation between front central regions and beta frequency at onset.

Having recorded more seizure from inferior frontal region (40,63%) and being the alpha band of frequency the most common for these regions, with the 50% of the seizures arising from these regions, we have the beta band of frequency as the most common of the sample, with the 59% of the cases. The front central regions are the responsible for this difference, as 50 % of the seizures with a beta onset arose from these regions, being the left front central region, F3, responsible in the 42 % of the cases. There seem to be a dominance of left hemisphere onset with beta and alpha frequency band at onset.

The division of the data in many locations produces the impossibility for linking these variables with statistical significance[21], but we can appreciate these differences in the following graphics:

Frequency at seizure onset by electrodes:

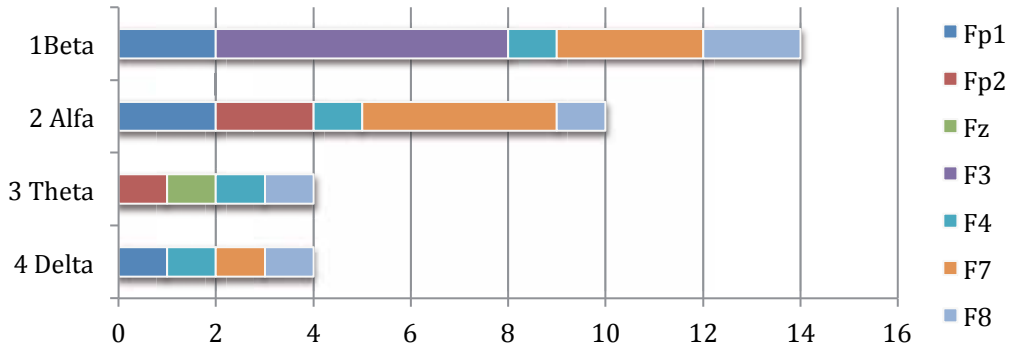


Fig. 91 Frequency at seizure onset by electrodes.

Frequency at seizure onset by homologue regions:

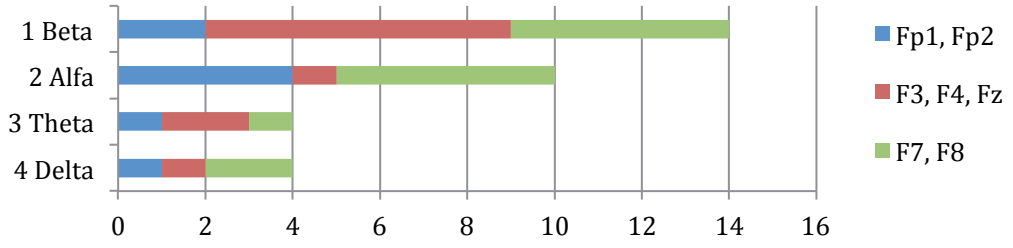


Fig. 92 Frequency at seizure onset by homologue regions.

[21]Statistical test in apendix

Frequency at seizure onset by hemisphere:

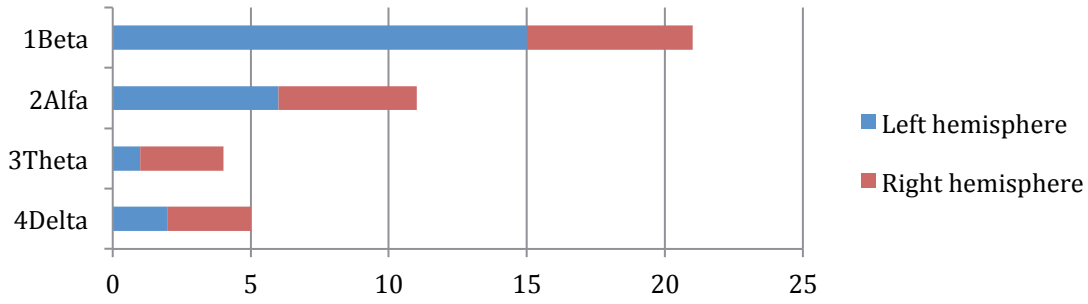


Fig. 93 Frequency at seizure onset by hemisphere.

6.3.5 Analysis of a potential relation between pathologic antecedents and focus location

We have studied the relation between the pathologic antecedents with the location of the focus:

1)-By electrodes

2) - By homologue regions

3) -By hemisphere

Afterwards, we have performed a complex analysis of the variables:

4) -Multi-factorial analysis, taking into account this two variables.

The cross tables regarding these variables are available in the “statistic appendix, problem 5”.

To sum up the data we can see the graphical aspect of the four analyses done.

1) Focus location (electrode) regarding pathologic antecedent

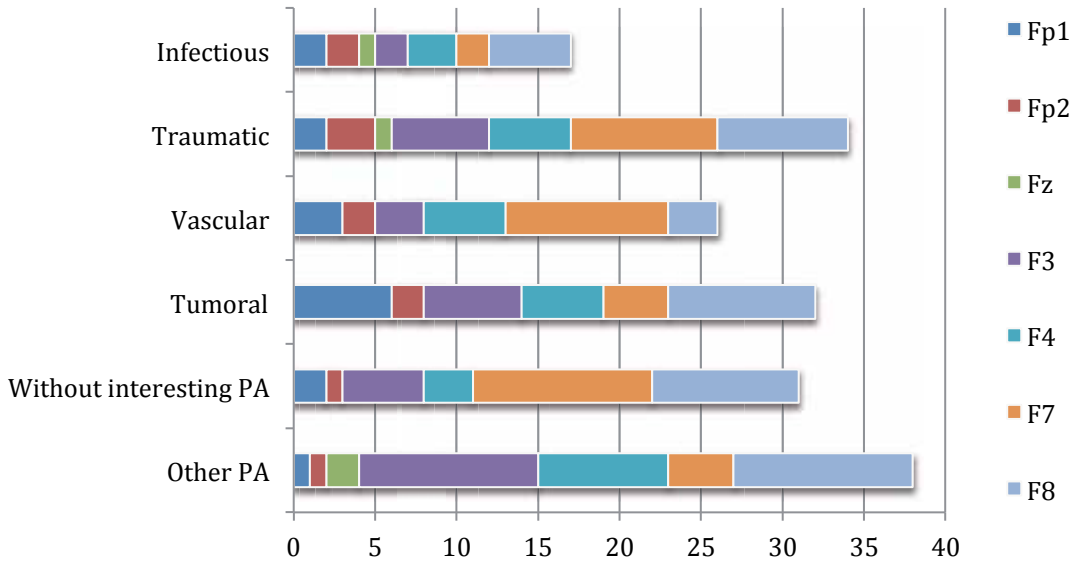


Fig. 94 Distribution of focus location (electrode maximal expression) regarding pathologic antecedent.

2) Focus location (by homologue regions) regarding pathologic antecedent

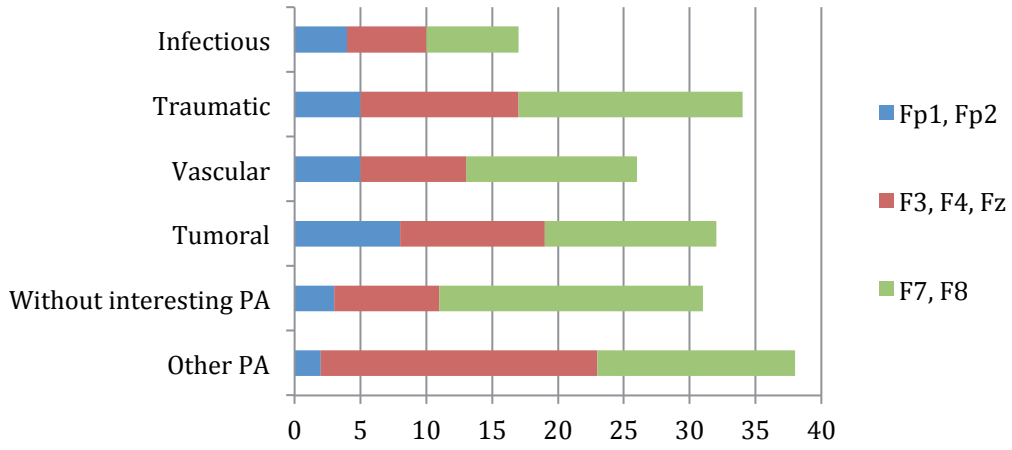


Fig. 95 Distribution of focus location (homologue regions) regarding pathologic antecedent.

3) Focus location (by hemisphere) regarding pathologic antecedent

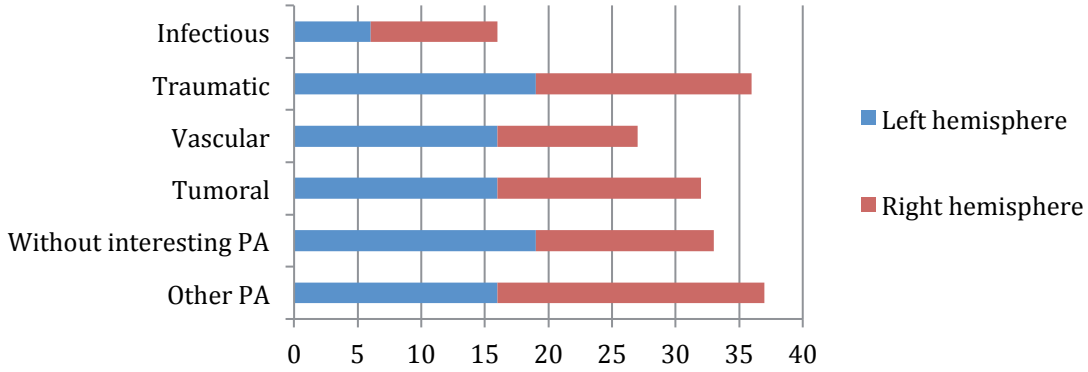


Fig. 96 Side focus location regarding pathologic antecedent.

4) The multi-factorial analyses did group the sample, automatically and regarding the data, into three groups:

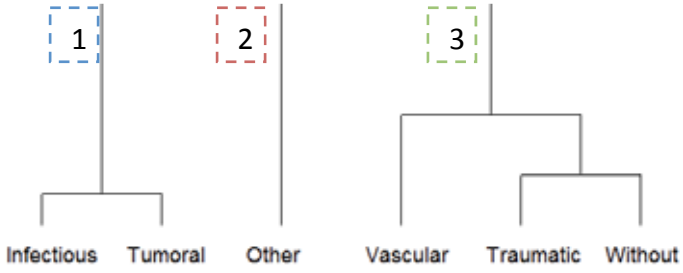


Fig. 97 Clusters.

The first group, mainly with an infectious or tumoral antecedent, had a tendency of association with focus located in both prefrontal region, with left side dominance, and did not link with focus on inferior frontal region, F7.

The second group, with “other” as the antecedent group defining this cluster, had frequently the focus located on left front central region, with statistical significance.

The third group, which most of “vascular” and “traumatic” cases as well as “without interesting antecedents” was found to have correlation with left inferior frontal regions, being significant statistically its relation with the left inferior frontal region and with negative association to front-central focus.

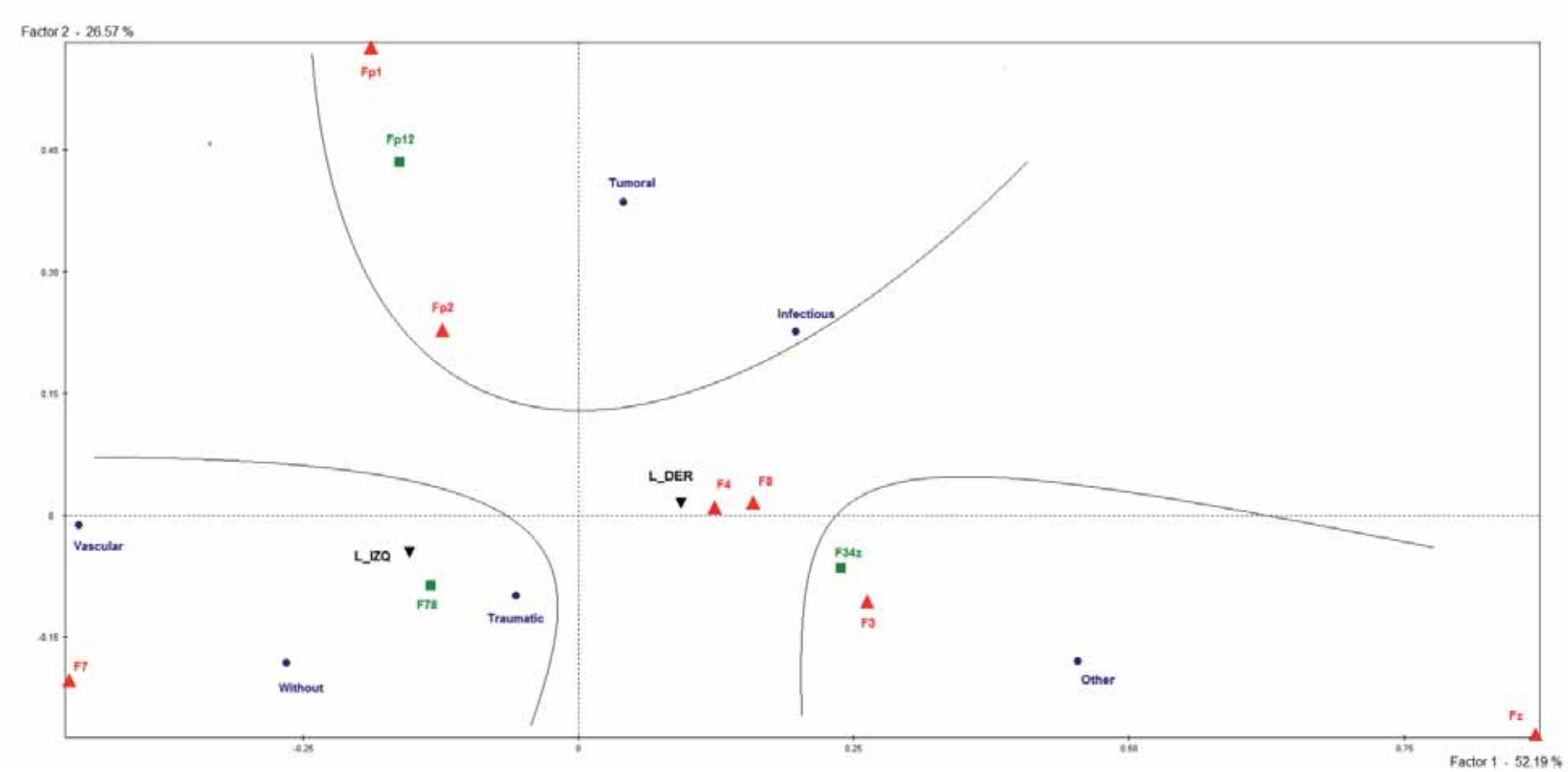


Fig. 98 Graphical view of the multi-factorial analyses of pathologic antecedent and focus location, including electrodes, homologue regions and hemisphere.

6.3.6 Analysis of a potential relation between the morphology of the interictal activity and pathologic antecedent.

For studying this complex relation, taking into account multiple factors, we performed a multiple correspondence analysis, regarding:

- The pathologic antecedent of the patient (Infectious, traumatic, tumoral, vascular, other, without antecedent)
- The morphology of the waveform (spike, simple sharp wave, diphasic sharp wave, poly-spikes)
- The activity after the epileptic wave (Isolated, followed by a slow wave, with a slow returning to the base-line, followed by an irregular slow wave)
- The voltage of the epileptiform activity (less than 50 µV, 50-100 µV, 100-200 µV, more than 200 µV)

Regarding all these factors the analysis automatically divided the population of the sample was into five groups:

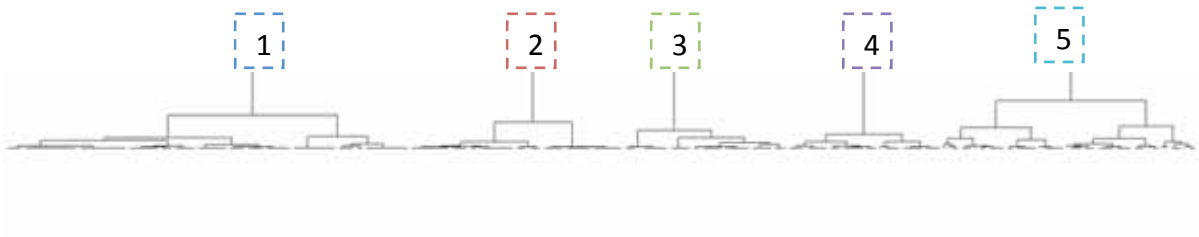


Fig. 99 Clusters

The **first group** was constituted by patients **without antecedents of interest and tumoral cases** (With the 68,89% of the cases without antecedents of interest and the 46,81 % of all the tumoral cases)**.**

Those had association (with statistic significance) to “Isolated waves”: 53,5 % of all isolated waves belong to this group and, at the same time 94,38 % of the waves of this group were isolated.

They were associated to “sharp morphology”, being in this group the 52,11 % of all “sharp waves” and at the same time the 83,15 % of the waves of this cluster were sharp waves.

About “amplitude”, there was a predominance of 50-100 µV, being the 51,72% of the waves of this voltage represented in this cluster, and also that 67,42% of the voltages in the cluster was of 50-100 µV.

We found also “**negative association**” with some other variables: “Traumatic” and “vascular” antecedent, voltages different from “50-100 µV”, a “diphasic sharp wave” or “spike” morphology and any “slow wave ” or “irregular slow wave” after the sharp wave.

The **second group** was had the 39,22% of “**traumatic” cases**, having relation to the following characteristics:

The more frequent waveform was “spike”, being the 38,46% of the spikes in this cluster and being the 47,17% of the waveforms in the group.

The waves were in the 100% of the cases of this cluster “isolated”, and representing the 33,76 % of all the isolated waves of the sample.

Regarding the “amplitude” the predominant voltage of this cluster was of “less than 50 µV”, as 86,79% of the waves in this group had this voltage, representing the 70,77 % of the waves of <50 µV of the sample.

The **negative association** of this group were: The sharp and diphasic sharp waves, followed by an irregular slow wave, a slow wave or a slow returning to the base-line; the “infectious” or “no interesting pathologic antecedent” and “voltages of 50-200 µV”.

The **third cluster** was constituted mainly by infectious cases, having the 73,91 % of all the infectious cases.

This group is related to “Sharp waves”, having the 26,06% of the sharp waves of the sample, which constitutes the 77,08% of the waveforms in the cluster.

Those, were followed by “irregular slow waves” in a 72,92% of the cases, and representing the 63,64 % of the “irregular slow waves” after an epileptic waveform. About the amplitude, there were related to “50-100 µV” in the 62,50% of the voltages recorded in this group, and representing the 25,86% of all the waves with this amplitude in the sample.

We found **negative association** with the following characteristics: Cases with tumoral or without interesting antecedents; “Isolated” waves or “followed by slow wave” or by the “slow returning to the base-line”; “Spike” morphology and “voltage of less than 50 µV”.

The **fourth cluster** was constituted by patients with “vascular antecedent”, having the 30% of these patients globally, and constituting the 37,50 % of the antecedents in this group. We found association with “spikes”, being the 87,50 % of the waves of the cluster, and containing the 43,08% of the spikes of the sample.

The EEG characteristics after the epileptic wave were a “slow wave” or an “irregular slow wave”.

We found **negative association** with “vascular” antecedent, with “simple and diphasic sharp wave”, with the “slow returning to the base line” and with “isolated” waves.

The **fifth** and last cluster did not link to any pathologic antecedent, and grouped the population regarding electroencephalographic characteristics:

It contains “diphasic sharp waves” as the main morphology, being the 67,50 % of the sample waves of this morphology, with two range of voltages: 100-200 µV and more than 200 µV; In this cluster are the 36,62% of the waves of 100-200 µV and the 80 % of the waves of more than 200 µV of the sample, representing the 65 and the 20 % of the cluster respectively.

We found that after the epileptic wave, there were a “slow returning to the base line”, containing the 91,18% of this characteristic in the all sample and constituting the 77,50 % of the cluster. There was also a slow wave, with the 37,5% of the entire sample, and constituting a 15 % in the cluster.

The **negative association** in this cluster were the “simple sharp waves”, “isolated” of followed by an “irregular slow wave”, with voltages of less than 100 µV.

This is the graphical description of the clusters previously explained

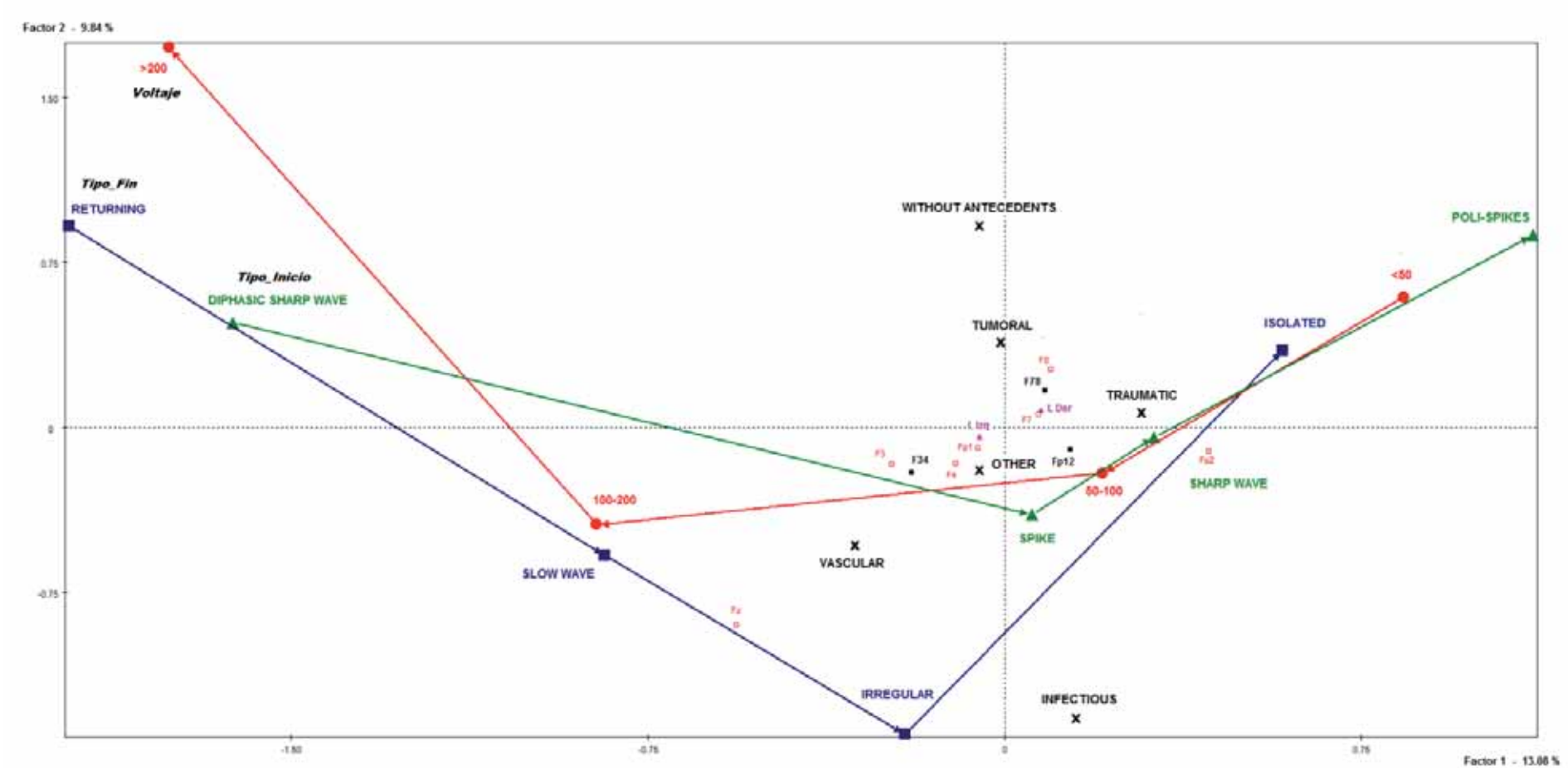


Fig. 100 Graphical view of the clusters result of the analyses.