Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

Usefulness of EEG for the differential diagnosis of possible transient ischemic attack ☆

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ARTICLE INFO

ABSTRACT

Objective: EEG value in possible transient ischemic attacks (TIA) is unknown. We aim to quantify focal slow wave activity (FSWA) and epileptiform activity (EA) frequency in possible TIA, and to analyse its contribution to the final diagnosis of seizures and/or definitive TIA.

Methods: Prospective longitudinal study of possible TIA patients evaluated at a tertiary centre during 36 months and with 1–3 months follow-up. EEG was performed as soon as possible (early EEG) and one month later (late EEG). A stroke neurologist established final diagnosis after reassessing all clinical and diagnostic tests.

Results: 80 patients underwent an early EEG (45.8 h after possible TIA): 52 had FSWA and 6 of them also EA. Early FSWA was associated with epileptic seizure or definitive TIA final diagnosis (p = .041). Patients with these diagnoses had more frequently early FSWA (19/23; 82.6%) than EA (6/23; 26.1%). 6/13 (46.2%) patients with epileptic seizure final diagnosis had EA.

Results: In the late EEG, 43 (58.1%) patients demonstrated persistent FSWA and 3 of them also EA. Persistent FSWA in the late EEG was more frequent in seizures than in TIA patients (91.7% vs. 45.5%). FSWA disappearance was associated with acute vascular lesion on neuroimage.

Conclusions: FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA, but did not distinguish between TIA and seizure patients. In patients with seizures, FSWA was more common than EA and its presence in the late EEG was more likely in patients with epileptic seizures than with TIA.

Significance: The majority of possible TIA patients with the final diagnosis of epileptic seizures do not have EA in the early or late EEG.

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1. Introduction

Neurological syndromes lasting less than 24 h include not only Transient Ischemic Attacks (TIA) but also other clinical entities such as epileptic seizures. The differential diagnosis between a transient ischaemic attack (TIA), an epileptic seizure or other tran-

sient neurological disturbances can be challenging and depends on the clinician's expertise (Calanchini et al., 1977; Castle et al., 2010; Ferro et al., 1996; Fonseca and Canhão, 2011; Kraaijeveld et al., 1984; Prabhakaran et al., 2008) and also on the available clinical information (Beniczky et al., 2012; Deacon et al., 2003; Fonseca and Canhão, 2011; Jin et al., 2014; Prabhakaran et al., 2008).

After extensive clinical investigation, approximately one-fourth of TIA patients are only labelled as "probable" or "possible TIA" (Fonseca and Canhão, 2011; Prabhakaran et al., 2008), defined as a clinical syndrome lasting less than 24 h that do not fulfil accepted criteria for TIA nor for another diagnosis, although a vascular origin cannot be excluded (Correia et al., 2015; Fonseca and Canhão, 2011). The main reasons for classification difficulties of possible TIA include odd accompanying symptoms (such as prickles/itching

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sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description (Fonseca and Canhão, 2011).

Diagnostic challenges between a TIA and an epileptic seizure include non-convulsive and inhibitory or negative seizures (Fisher, 1978; Kaplan, 1993; Lee and Lerner, 1990; Primavera et al., 1993) and TIA with positive symptoms, such as "limb-shaking" TIA (Fisher, 1962; Muraga, 2016). Further hampering this distinction is the possibility of epileptic seizures caused by a TIA (Cocito and Loeb, 1989; Ferracci et al., 2000; Primavera et al., 1993) and the existence of other mimics with a non-vascular and non-epileptic origin (Carreño, 2008).

De Reuck and Van Maele (De Reuck and Van Maele, 2009) analysed the role of EEG in the differential diagnosis of a TIA versus an inhibitory seizure and concluded that an early EEG is crucial in their investigation. However, the type and frequency of electroencephalographic abnormalities in possible TIA and its value in the distinction between epileptic seizures and TIA is not exactly known. In this study we aim to respond to the following:

1) What is the frequency of electroencephalographic abnormalities in patients with possible TIA and to which clinical/imaging characteristics are they associated?
2) What is the percentage of patients with possible TIA with a final diagnosis of epileptic seizure or definitive TIA and which electroencephalographic characteristics differentiate these diagnoses?

2. Methods

Prospective longitudinal study of patients with a diagnosis of possible TIA evaluated at the TIA Clinic or admitted to the Stroke Unit of the Hospital de Santa Maria (HSM-CHLN), between November 2010 and October 2013. The Ethics Committee "Comissão de Ética para a Saúde" of the HSM-CHLN approved this study.

As inclusion criteria, the patients had to meet the clinical criteria for an initial diagnosis of possible TIA (see definition below) and gave their informed consent. Symptoms suggestive of brainstem/cerebellum involvement were exclusion criteria. The study design is described in Fig. 1.

2.1. Standardized clinical and ancillary evaluation (Correia et al., 2015; Fonseca and Canhão, 2011)

Patients were referred to the TIA Clinic by the HSM-CHLN emergency department (ED) or their family doctor. In the ED, patients underwent routine blood tests, ECG and brain non-contrast CT scan (CT) and were prescribed with antiplatelet agents and statins. In the daily TIA Clinic, a stroke neurologist performed a structured clinical interview and physical and neurological examination. On the same day, patients underwent carotid and vertebral duplex scans, transcranial Doppler and blood tests. Transthoracic or transesophageal echocardiography or 24 h Holter were ordered, whenever considered necessary. When possible, an MRI including diffusion-weighted imaging (DWI) was done. A neuroradiologist reported all imaging exams. The stroke neurologist, after review of all exams, decided about further treatment, the need for hospitalization and booked the patient for a follow-up appointment one to three months later.

Patients with a possible TIA were admitted to the Stroke Unit, from the ED or TIA Clinic, whenever a definitive diagnosis of TIA was not established, symptoms had not cleared or the patient was judged to be at a high risk of recurrence. The evaluation of admitted patients and their follow-up was similar to those in the TIA Clinic.

The following symptoms associated with possible TIA were systematically recorded: motor, sensory, speech disturbances, partial
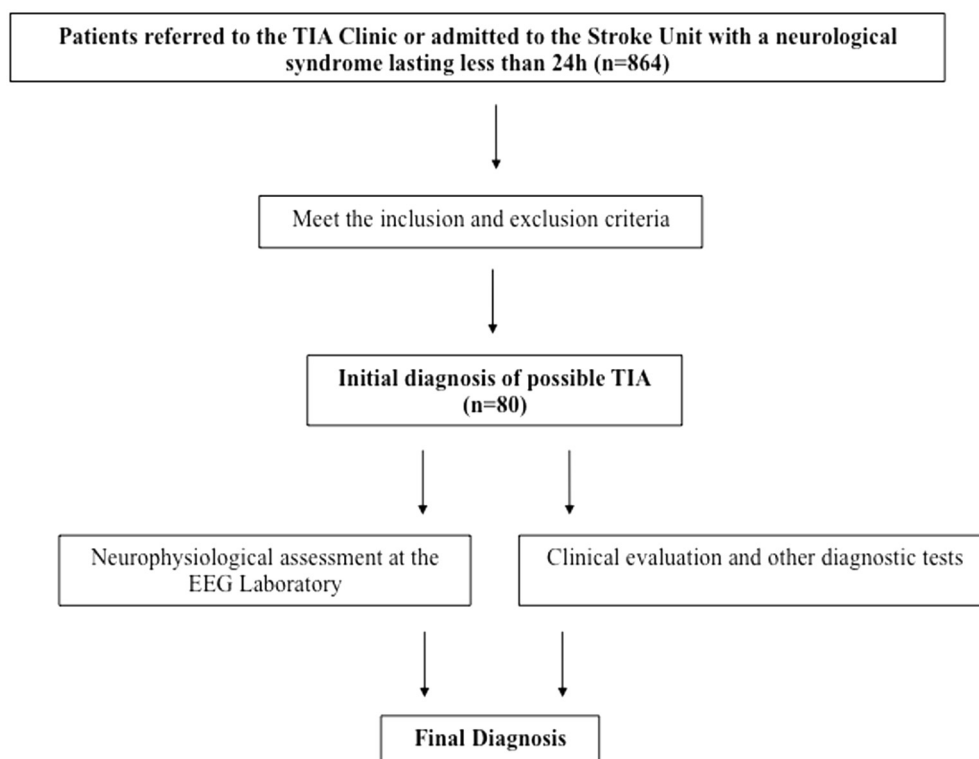

Fig. 1. Study Design. TNA – Transient Neurological Attack/TIA – Transient Ischaemic Attack.

or total amnesia for the event, consciousness disturbance, and confusional period. Positive symptoms were defined as the occurrence of involuntary movements, sensory symptoms apart from numbness or anaesthesia (such as tingling, stinging, prickling, burning sensations or pain) and visual delusions (palinopsia, polyopia, micro, macro or metaphormopsia), simple (e.g.: lights, spots, oscillating lines with bright, sparkle or colour) or complex hallucinations. The presence of a Jacksonian march of symptoms was considered whenever there was sequential spread of motor (or sensory) symptoms beginning at a specific body region to involve other body parts, accordingly to an electrical disturbance spreading through the homunculus of the motor (or sensory) cortex (Larner, 2011)

Patients were classified in 5 symptomatic groups, not mutually exclusive, taking into account symptom characteristics and their different specificity for the final diagnosis:

1. Motor symptoms
2. Positive phenomena and/or march of symptoms (more frequent in seizures than in TIA)
3. Sensory and/or visual symptoms (posterior brain symptoms)
4. Speech disturbance
5. Amnesia for the event and/or consciousness disturbance and/or confusional period (including consciousness, level or content, disturbance symptoms)

2.2. Diagnostic criteria

The diagnosis of each patient was defined according to the following criteria:

- *Initial diagnosis*: established at the end of the first observation in TIA Clinic or Stroke Unit by a stroke neurologist (PC).
- Final diagnosis: established after the end of the study by a stroke neurologist (PC), taking into account clinical reassessment 1–3 month after the clinical episode, and the result of all diagnostic tests (including early and late EEG). Patients were reclassified in the following final diagnosis groups: TIA; possible TIA; epileptic seizures; other TIA mimic (including migraine; psychiatric disturbance; others). Another neurologist trained in epilepsy (CB), having had access to the same clinical and complementary information, independently reclassified the patients in the same final diagnosis groups.

The following definitions were used for the diagnosis (initial and final):

- Transient ischaemic attack (*TIA*): Clinical syndrome characterized by sudden focal neurological symptoms, presumed to be of vascular origin, that lasted less than 24 h (WHO, 1975), regardless of whether or not brain imaging showed a recent ischaemic lesion. This diagnosis group included patients with an acute onset of temporary (less than 24 h) neurological dysfunction consistent with focal brain ischemia and with supportive or no contradictory complementary diagnostic tests including brain imaging demonstrating or not an acute vascular ischemic lesion. The typical history for a TIA was a swift onset (no symptoms to maximal symptoms in less than five minutes) of a motor defect, sensory defect, aphasia, loss of vision in one eye or in part of one eye, homonymous hemianopia, or a combination of the above (WHO, 1975). In these patients an epileptic seizure or another TIA mimic did not cause the clinical syndrome.
- Possible transient ischaemic attack (*possible TIA*): Neurological syndrome lasting less than 24 h that do not fulfil international accepted criteria for TIA nor the criteria for a specific mimic

diagnosis, although a vascular origin could not be excluded (Correia et al., 2015; Fonseca and Canhão, 2011). This diagnosis group included patients with odd accompanying symptoms (such as prickles/itching sensations, rigid postures or movement of the limbs), march of symptoms, consciousness disturbance or amnesia with focal symptoms, multiple stereotyped episodes, positive visual phenomena, isolated speech disturbance/confusion and focal symptoms plus panic or anxiety and paucity of details in the symptoms description, (Fonseca and Canhão, 2011) without imaging/laboratory evidence of ischemic cerebral pathology (Kidwell and Warach, 2003) nor of another TIA mimic.
- Transient ischaemic attack mimic (*TIA mimic*): Focal neurological syndrome lasting less than 24 h, for which a non-vascular cause was definitively established according to predefined criteria (Fonseca and Canhão, 2011) (e.g.: migraine with aura) (Headache Classification Subcommittee of the International Headache Society, 2004), metabolic syndrome, transient global amnesia (Caplan, 1985; Hodges and Warlow, 1990), panic attack (American Psychiatric Association, 2000), somatoform disorder (American Psychiatric ssociation, 2000). An epileptic seizure can also be a TIA mimic but was classified separately in this study.
- Epileptic seizure (*seizure*): transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain (Fisher et al., 2014). This diagnosis group included patients with positive motor, sensitive, or sensorial symptoms (as previously described) and also with motionless, unresponsive or automatic behaviour according to stereotyped focal seizures and/or successful response to antiepileptic treatment, epileptiform activity on EEG (D'Ambrosio and Miller, 2010) or the occurrence of an unequivocal seizure in the follow-up. In these patients a TIA and a TIA mimic have been excluded. Accordingly, in patients with possible TIA, the final diagnosis of seizure was established (if other diagnoses were considered excluded after all diagnostic tests and clinical reassessment) in two different circumstances: 1) in patients with possible seizure semiology and epileptiform activity in the EEG; 2) in patients with possible seizure semiology and no epileptiform activity in the EEG but with additional (or better described) clinical events clearly indicative of seizures during the follow-up.

TIA and epileptic seizures were considered the two final diagnoses of interest for this study.

2.3. Neurophysiological assessment

All patients underwent a 64-channel video-EEG using a digital Nihon-Kohden device and electrodes placed in accordance with the international 10/10 system and following national and international recommendations (American Clinical Neurophysiology Society, 2006a,b; Flink et al., 2002; Martins da Silva et al., 2011; Nuwer et al., 1998) in two different periods: 1) As soon as possible after the possible TIA (*early EEG*); 2) One month after (*late EEG*). We intend to repeat EEG, based on guidelines reporting that repeating EEG may be helpful when the diagnosis of epilepsy is unclear (National Institute for Health and Care Excelence, (NICE), 2012)). One month after the clinical event was the date chosen for EEG repetition to match the scheduled follow-up clinical visit.

The record had a maximum duration of 60 min, including an eye closed wake resting condition and eye open, hyperventilation and photic stimulation manoeuvres.

Two clinical neurophysiologists (CB + RP), blinded for the final diagnosis, interpreted the records. Discrepancies were decided by consensus. All EEG records were evaluated for the presence of

the following abnormalities: background activity slowing (Noachtar et al., 1999); asymmetry (Hirsch et al., 2013); suppression (focal, hemispheric or diffuse) (Hirsch et al., 2013); focal slow wave activity (including focal and regional concept) (Noachtar et al., 1999); epileptiform activity (Noachtar et al., 1999), periodic discharges (Hirsch et al., 2013) and others.

The two EEG variables of interest for the present study were *Focal Slow Wave Activity (FSWA)* and *Epileptiform Activity (EA)* (Fig. 2). The following operational definitions were used:

- *FSWA:* continuous or intermittent slow activity i.e. theta and/or delta band activity (Noachtar et al., 1999) limited to an area of the brain or scalp region (includes the concept of focal and regional (Noachtar et al., 1999)).
- *EA:* (Noachtar et al., 1999): transients clearly distinguishable from background activity, with a characteristic spiky morphology at a conventional time scale, duration of 70–200 ms (sharp wave) or from 20 to under 70 ms (spike) and a main component generally negative relative to other areas.

FSWA evolution between early and late EEG was also analysed and considered "*persistent*" if existing in both exams (even if intermittently), "*transient*" if present in the early but absent in the late and "*absent*" if non-existent in both EEG.

2.4. Statistics

Univariate descriptive statistics were used for categorical and continuous variables. Bivariate analysis was performed using χ^2 test, Fisher's exact test or t-student or Mann-Whitney test, as appropriate. The level of significance was established at $\alpha < 0.05$ (two-tailed).

To define independent predictors of neurophysiological outcomes, significant variables at $p < .05$ in the bivariate analysis were tested in multivariate analysis using a stepwise binomial logistic regression with backward elimination. A Hosmer and Lemeshow test assessed the calibration of the model and the Receiver Operator Characteristic (ROC) curve its discriminative capacity.

As a measure of final diagnosis interobserver agreement we used Cohen's kappa statistic.

The statistical analysis was performed using SPSS software version 21 for Mac.

3. Results

Eighty patients were included with the initial diagnosis of possible TIA. Table 1 describes the demographic, clinical, imaging and electroencephalographic characteristics of these patients.

3.1. Frequency of EEG abnormalities

In the early EEG, 52/80 patients (65%) had FSWA, 6 of them also EA (6/80 7.5%) and 7/80 (11.7%) other abnormalities (increase of beta activity in 5 and diffuse slowing of background activity in 2). The EEG record was reported as normal in 21/80 patients (26.2%).

After one month, 74 patients (92.5%) repeated the EEG, which was normal in 25 (33.8%). In this record, 44/74 (59.5%) patients had FSWA. FSWA evolution (Table 1) was demonstrated persistent in 43 (58.1%), transient in 6 (8.1%) and absent in 24 (32.4%) patients. In one patient (1.4%), FSWA only emerged in the late EEG. Only 3 of the 6 patients with EA in the early EEG retained this activity in the late EEG. No patient showed EA in this exam when not present in the early EEG.

At the time of the early EEG (Supplementary file 1), 11 patients (13.8%) were being treated with antiepileptic drugs (AED). During follow-up, 7 patients (3 with EA in early EEG) were prescribed AED (6 for epileptic seizures and 1 for migraine). At the time of the late EEG, 18 patients (24.3%) were on AED.
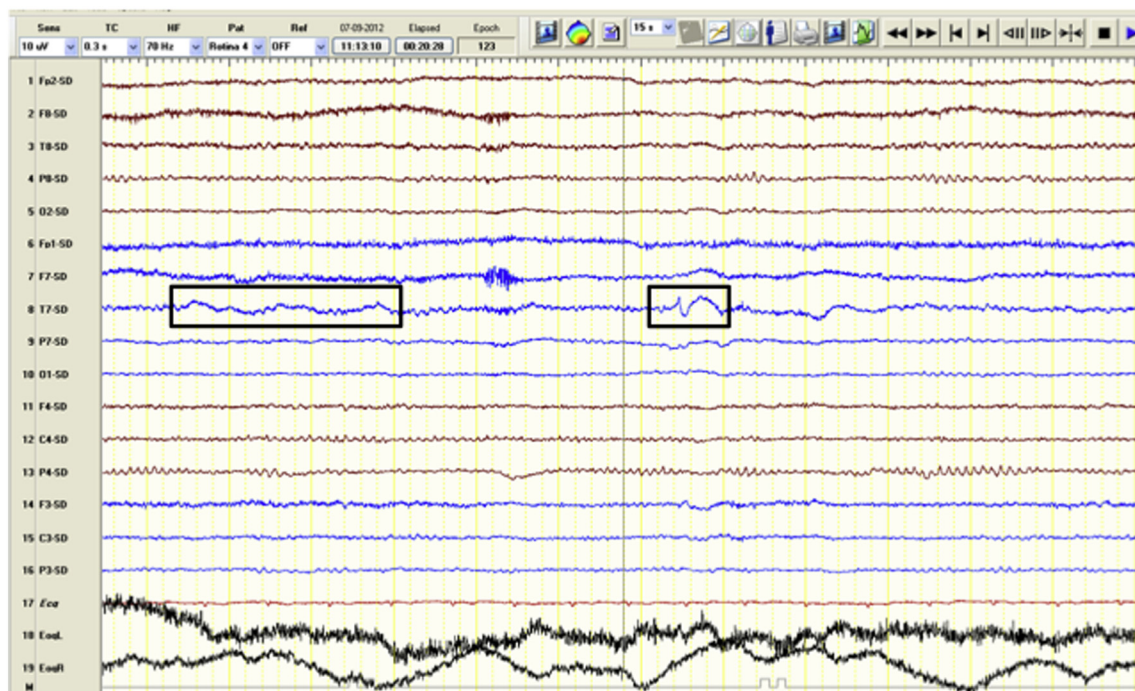

Fig. 2. Focal Slow Wave Activity and Epileptiform activity. Source derivation montage of a 15 mm/s EEG page. Left Black Square highlights Focal Slow Wave Activity and right Black Square identifies Epileptiform Activity (abrupt wave followed by a slow wave).

Table 1
Demographic, clinical, imaging and electroencephalographic characteristics of patients with the initial diagnosis of possible TIA.

Demographic characteristics		
Male/Female	36/44 (45%/55%)	
Age (Years)	Mean: 65.5 (S.D. 14.4); Median: 68.5	
Clinical characteristics		
Sudden onset (<1 min)	54 (71.1%)	
Motor symptoms	20 (25%)	
Positive symptoms and/or March of symptoms	40 (50%)	
Sensory symptoms and/or visual symptoms	43 (53.8%)	
Speech disturbance	43 (53.8%)	
Amnesia and/or consciousness disturbance and/or confusional period	36 (45%)	
Number of previous episodes	Mean: 2.1 (S.D. 1.3); Median: 2	
Mean duration of the last episode (hours)	Mean: 2.4 (S.D. 4.8); Median = 0.5	
Time between symptoms and EEG (hours)	Mean: 45.8 (S.D. 37.5); Median: 37.5	
Imaging characteristics		
MRI (n = 43/53.8%)	DWI+	4 (9.3%)
	Another lesion	22 (51.2%)
Electroencephalographic characteristics		
Early EEG (n = 80)	FSWA	52 (65%)
	EA	6 (7.5%)
Late EEG (FSWA evolution; n = 73/91.2%)	Persistent FSWA	43 (58.9%)
	Absent or transient FSWA	30 (41.1%)

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity, DWI+ – acute vascular lesion on MR diffusion-weighted imaging, S.D. – Standard deviation.

3.2. Clinical/Imaging characteristics associated with EEG abnormalities

3.2.1. Age

Both patients with FSWA in the early EEG and patients with demonstrated persistent FSWA in the late EEG were respectively 12.3 ± 3.4 (t(43.43) = 3.63, p = .001) and 11.3 ± 3.1 years (t(46.52) = 3.66, p = .001) older than the remaining sample.

There was no significant difference in the mean age of patients with or without EA in the EEG (t(78) = −1.17, p = .902).

3.2.2. Neurological syndrome characteristics

No significant associations were found between the variables of the two EEG and the number of previous episodes, duration or the time interval between the clinical event and the EEG.

The electroencephalographic characteristics of the different symptomatic groups under study are depicted in Table 2.

In the early EEG, FSWA was associated with amnesia for the event and/or consciousness disturbance and/or a confusional period (Table 2). In this exam, 5 patients with EA (83%) had a clinical syndrome with speech disturbances and 4 (66.7%) at least one of the following: amnesia for the event, consciousness disturbance and/or confusional period. EA was significant associated with a neurological syndrome with consciousness disturbance (Fisher's exact test, p = .040, OR = 6.59, 95% CI: 1.11–39.15).

In the late EEG, persistent FSWA was associated with the presence of speech disturbances (χ^2 = 7,41, p = .006, OR = 3.77, 95% CI: 1.42–9.97) and transient FSWA with a confusional period (Fisher's exact test, p = .047, OR = 6,25, 95% CI: 1.04–37.37).

In a binomial logistic regression model, FSWA was no longer predicted (p = .499, OR = 1.47, 95% CI: 1.02–1.11) by "amnesia and/or consciousness disturbance and/or confusional period" when adjusted for age (χ^2(2) = 14.00, p < .0005; NagelkerkeR^2 = 22.1%; Hosmer-Lemeshow test, p = .839; AUC = 0.74, p < .0005, 95% CI: 0.62–0.87).

Persistent FSWA in the late EEG was independent predicted by both age (p = .002, OR = 1,08, 95% CI: 1.03–1.13) and "speech disturbances" (p = .02, OR = 3.54, 95% CI: 1.22–10.28) in the logistic regression model (χ^2(1) = 17.73, p < .0005; NagelkerkeR^2 = 31.4%; Hosmer-Lemeshow test, p = .714; AUC 0.80; p < .0005, 95% CI: 0.69–0.90).

3.2.3. Imaging characteristics

No differences in EEG variables were observed in patients with and without normal MRI. Among patients with an acute vascular lesion in the MRI (DWI+), three (75%) had FSWA in the early EEG and in two of them (66.7%) this activity disappeared in the late EEG (Fisher's exact test, p = .011).

3.3. Final diagnosis of epileptic seizure or definitive TIA in patients with possible TIA

After all diagnostic tests and clinical reassessment, patients with possible TIA were reclassified in a final diagnosis (Fig. 3).

Thirteen patients were diagnosed with epileptic seizures (16.3%) and 11 (13.8%) with definitive TIA by the stroke neurologist (PC). One patient had a final dual diagnosis of definitive TIA and epileptic seizures. This patient was discharged from the Stroke Unit with a TIA diagnosis. However, in the follow-up appointment the patient reported different episodes that were then diagnosed as partial complex seizures.

3.3.1. Interobserver agreement

The two neurologists agreed in the diagnosis of 59 patients (73.8%). The interobserver concordance in the final diagnosis was good (k = 0.627, p < .0005, 95% CI: 0.485–0.769). In the analysis of the diagnosis of seizure (vs. non-seizure), the two classifiers agreed in 73 patients (91.2%). The interobserver agreement was good (k = 0.707, p < .0005, 95% CI: 0.503–0.911). Also, for the diagnosis of definitive TIA (vs. non definitive TIA) the interobserver agreement was good (k = 0.789, p < .0005, 95% CI: 0.587–0.991), with a concordant diagnosis in 76 patients (95%).

3.3.2. Clinical/Imaging characteristics associated with the final diagnosis of interest

No significantly mean age difference was found between patients with final diagnosis of epileptic seizures or TIA and other final diagnosis (t(65.85) = 1.474, p = .145).

Clinical and EEG characteristics of patients with the final diagnosis of seizures and definitive TIA are displayed in Table 3.

Of the evaluated symptoms, only the existence of a Jacksonian March of symptoms was more frequent in seizure patients (n = 7;

Table 2
Electroencephalographic abnormalities in different symptomatic groups.

Type of Symptoms	Motor		Positive and/or March of symptoms		Sensory and/or Visual		Speech disturbances		Amnesia and/or Impaired consciousness and/or Confusional period	
Early EEG (n = 80/100%)	n = 20		n = 40		n = 43		n = 43		n = 36	
	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	N	p, OR, 95% CI
FSWA (n = 52)	12	.588, 0.750, 0.26–2.13	24	.348, 0.64, 0.26–1.62	23	**.020, 0.320, 0.12–0.85**	32	.057, 2.47, 0.96–6.34	28	**.030, 2.92, 1.09–7.81**
EA (n = 6)	3	.162, 3.35, 0.62–18.16	2	.675, 0.47, 0.08–2.75	0	**.008, RR = 0.42, 0.32–0.55**	5	.209, 4.74, 0.53–42.53	4	.401, 2.62, 0.45–15.24
Late EEG (FSWA evolution; n = 73/91.2%)	n = 18		n = 37		n = 39		n = 40		n = 34	
	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI	n	p, OR, 95% CI
Persistent FSWA (n = 43)	10	.739, 0.83, 0.28–2.44	20	.393, 0.67, 0.26–1.70	16	**.001, 0.18, 0.06–0.51**	29	**.009, 3.58, 1.34–9.52**	23	.156, 1.99, 0.76–5.16
Absent or transient FSWA (n = 30)	8		17		23		11		11	

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity.
Bold values represent p < 0.05.
* The different symptomatic groups are not mutually exclusive. The bivariate statistical analysis was performed using χ2 test or Fisher's exact test having as independent variable each symptomatic group and as dependent variable each EEG characteristic.
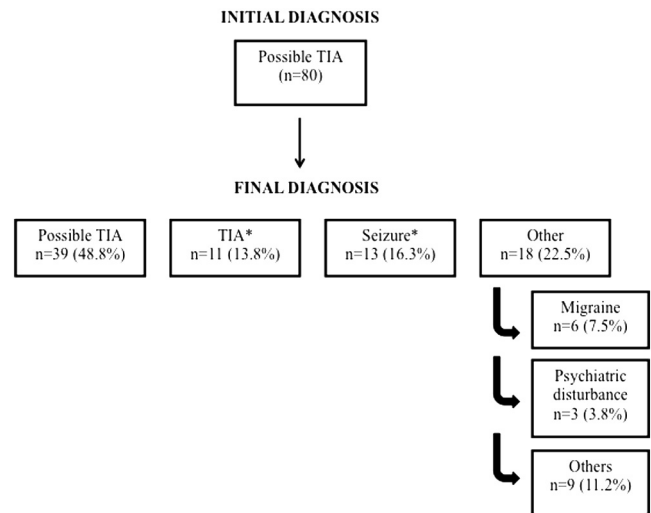

Fig. 3. Reclassification of possible TIA. *A patient classified as TIA had the concomitant diagnosis of epileptic seizures (partial complex seizures) in the clinical follow-up.

50%) than in patients with definitive TIA (n = 1; 9.1%) (Fisher's exact test, p = .027, OR = 14.000, 95% CI: 1.329–147.429).

MRI was performed on eight (66.7%) patients with epileptic seizures and five (45.4%) patients with the final diagnosis of definitive TIA, four of whom (80%) had an acute vascular lesion in the DWI.

3.4. Electroencephalographic characteristics in patients with epileptic seizure and definitive TIA diagnosis

FSWA in the early EEG was differently distributed between final diagnosis groups (p = .027). Furthermore, FSWA in the early EEG was associated with the final diagnosis of epileptic seizure or definitive TIA compared to other type of final diagnosis (19/23 patients versus 33/57 patients; p = .041; OR 3.46; 95% CI 1.04–11.46).

The only significant EEG difference between patients with epileptic seizures and definitive TIA was a different evolution of FSWA between the early and the late EEG (Table 3). The chance of persistent FSWA in the late EEG was significantly greater (13.2 times higher) in a patient with an epileptic seizure than in a patient with TIA. In fact, the majority of patients with seizures (91.7%) maintained the FSWA between the two examinations while the same only occurred in less than half (45.5%) of TIA patients. Furthermore, absent or transitory FSWA was less frequent in patients with seizures (8.3%) than with TIA (54.5%).

Although a higher percentage of patients with epileptic seizures had EA, this difference was not statistically significant. Of the 13 patients who had the final diagnosis of epileptic seizures, six (46.2%) had EA in the early EEG.

4. Discussion

FSWA was the commonest EEG abnormality found in the early EEG of patients with possible TIA, but did not distinguish between TIA and seizure patients. In patients with seizures, FSWA was more common than epileptiform activity and its presence in the EEG one month later was more likely in patients with epileptic seizures.

In this work, EEG abnormalities were frequent, occurring in 73.8% of the patients. FSWA was the most common, although others could be identified. This percentage is similar to that found by De Reuck and Van Maele (2009) in patients with inhibitory seizures (76%), but rather different from that of patients with defini-

Table 3
Clinical characteristics of the patients with a final diagnosis of seizures and TIA.

	Final diagnosis		p
	Seizures* (n = 12)	TIA* (n = 11)	
Age in years (SD)	68.2 (10.4)	68.9 (9.1)	.874
Total duration of symptoms in hours (SD)	1.3 (1.5)	1.8 (2.6)	.695
Number of previous episodes (SD)	2.8 (1.8)	2.4 (1.6)	.874
Time between symptoms and EEG in hours (SD)	34.6 (32.3)	38.2 (26.1)	.561
Symptoms			p, OR, 95% CI
Motor symptoms	4 (33.3%)	6 (54.5%)	.414 0.417, 0.08–2.25
Positive symptoms and/or March of symptoms	7 (58.3%)	3 (27.3%)	.214 3.73, 0.65–21.58
Sensory and/or visual symptoms	3 (25%)	5 (45.4%)	.400 0.40, 0.07–2.34
Speech disturbances	8 (66.7%)	8 (72.7%)	1.000 0.75, 0.12–4.49
Amnesia and/or Consciousness disturbance and/or Confusional period	7 (58.3%)	5 (45.4%)	.537 1.68, 0.32–8.76
Electroencephalographic characteristics			
Early EEG	FSWA	11 (91.7%)	8 (72.7%)	.317 4.12, 0.36–47.30
	EA	5 (41.7%)	1 (9.1%)	.155 7.14, 0.68–75.22
Late EEG (FSWA evolution)	Persistent FSWA	11 (91.7%)	5 (45.4%)	.027 13.20, 1.24–140.68
	Absent or transient FSWA	1 (8.3%)	6 (54.5%)	

EA – Epileptiform Activity, FSWA – Focal Slow Wave Activity, TIA – Transient Ischaemic Attack.
* The patient who had the final dual diagnosis of TIA and seizures is included in this table only in the TIA group because the clinical episode that provoked the admission to the Stroke Unit had the final diagnosis of TIA.

tive TIA (7.6%) in the same study. Unlike this Belgian study, we did not recognise early EEG differences between epileptic seizure and definitive TIA patients. There are some plausible explanations for this apparent discrepancy between the two studies, namely time until EEG and age. Neurological syndromes lasting less than 24 h are, by definition, time-limited events of neurological dysfunction and, for that reason, time interval between clinical manifestations and EEG might influence the presence or the type of electroencephalographic abnormalities. In the De Reuch and Van Maele study, 100% of patients with seizures but less than half of patients with definitive TIA underwent an EEG in the first 24 h. Furthermore, temporal slowing is a frequent finding in older patients (Samson-Dollfus et al., 1991) and seizure patients were older than TIA patients in the same study. In our series, time until EEG and age were not significantly different in patients with seizures and with TIA.

In this series of possible TIA patients, epileptic seizures were the most common final diagnosis, followed by definitive TIA. Approximately one half of the patients remained undiagnosed, clearly showing the differential diagnosis difficulty of possible TIA and the need for complementary strategies supporting the classification of these undefined events (Dolmans et al., 2015). Sequential spread of symptoms according to the homunculus of the motor (or sensory) cortex were associated with the diagnosis of epileptic seizures, in agreement with the "Jacksonian march" characteristic of focal seizures (York and Steinberg, 2011).

In our work, patients with early FSWA had a higher probability of subsequent diagnosis of epileptic seizures or definitive TIA, not explained by a different mean age between final diagnosis groups. Furthermore, a higher percentage of patients with these final diagnoses had early FSWA compared to early EA (82.6% vs. 26.1%, respectively). Although FSWA is not specific to the final diagnosis, it was informative and more sensitive than EA. In line with these results, a patient with a possible TIA with early FSWA should be further investigated and followed-up.

Six patients (7.5%) had EA in the early EEG, a higher percentage than the reported frequency of false-positive (0.5–1%) in asymptomatic individuals (Gregory et al., 1993; Robin et al., 1978). The percentage of patients with a definite diagnosis of epileptic seizures and EA in the early EEG (46.2%) is within the range of sensitivity reported for EEG (26 to 56%) as a diagnosis test for epilepsy (National Institute for Health and Care Excelence, (NICE), 2012). Still, it is possible that AED prescription in 14% of the patients reduced the probability of finding EA in the early EEG (Jawad

et al., 1986; Milligan et al., 1982; Pro et al., 2009; Rocamora et al., 2006). Furthermore, focal seizures arising from small foci or deep foci for the recording electrodes may not have a surface EEG correlate. It is known that the repetition of EEG can be useful when the diagnosis of epilepsy is not clear (National Institute for Health and Care Excelence, (NICE), 2012; Scottish Intercollegiate Guidelines Network, 2015). Salinsky and collaborators (Salinsky et al., 1987) showed that 50% of epilepsy patients had EA in the first EEG, 84% in the third EEG and 92% in the fourth EEG. However, in our study, the repetition of the EEG did not improve the EEG value in EA detection, as would be expected. There are two possible reasons for this finding. On the one hand, there is the already discussed effect of AED in the intercritical EA (Jawad et al., 1986; Milligan et al., 1982; Pro et al., 2009; Rocamora et al., 2006). In fact, the percentage of medicated epileptic seizures patients by the time of late EEG was greater than in early EEG (92.3% vs. 38.5%). On the other hand, the likelihood of finding EA in the EEG seems to decrease over time after a paroxysmal event (Sundaram et al., 1990). The lack of a significant difference in the incidence of EA in the EEG of patients with the final diagnosis of seizure and TIA is likely to be due to small patient numbers in each subgroup.

The time evolution pattern of FSWA was significantly different between the two final diagnostic groups (seizures and TIA), as patients with seizures more often had FSWA persisting in the late EEG. The high percentage of epileptic seizure patients with early FSWA and the persistence of FSWA in the late EEG in these patients, may represent a neurophysiologic marker of the existence of an enduring predisposition to generate epileptic seizures (Fisher et al., 2005, 2014). In fact, FSWA has been described in patients with epilepsy as a good marker of the epileptogenic network and the ictal onset zone (Brigo, 2011; Di Gennaro et al., 2003; Tao et al., 2011; Vanrumste et al., 2005). In contrast, patients with definitive TIA had a different FSWA time evolution pattern: either they never had FSWA in the early EEG or the FSWA was no longer present in the late EEG, in accordance with what was described in transitory cerebral ischemia due to carotid compression (Meyer et al., 1965).

This work has some strengths, such as: 1) it compares EEG differences between patients who initially had transient neurological symptoms and a not yet established neurological diagnosis, reflecting the clinical practice diagnostic question - is the EEG useful when the diagnose is unknown?; 2) EEG readers were blind to the final diagnosis, which was established only after the EEG report; 3) no patients were lost for clinical follow-up and only a

few (7.7%) for the EEG follow-up; and 4) the high final diagnosis interobserver agreement gives robustness to the results. Nevertheless, this study also has some limitations, in particular: 1) it was hospital-based limiting generalization to other clinical settings; 2) A time-based TIA definition was used, so these results may not apply to tissue-based defined TIA (Albers et al., 2002; Easton et al., 2009); 3) Only two EEG abnormalities were variables of interest in this study but others could be considered; 4) the sample size was modest, which limits the statistical power for some comparisons.

5. Conclusions

In the early EEG, the majority (58.3%) of patients with a final diagnosis of an epileptic seizure did not have EA. FSWA in the early EEG occurred whether the patient suffered a seizure or TIA (and was more often present than EA following a seizure), but in the EEG performed 1 month after the clinical episode was more likely to indicate that the initial event was a seizure.

Acknowledgments

Funding

Conflict of interest

The authors have completed the Unified Competing Interests form and declare that: Dr. Bentes received the 2012 Research Grant in Cerebrovascular Diseases (Scientific Promoter: Sociedade Portuguesa do AVC - Sponsor: Tecnifar). Dr. Ferro reports personal fees from Boehringer Ingelheim, and personal fees from Daiichi Sankyo, outside the submitted work. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cnp.2017.10.001.

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