Epilepsy & Behavior 88 (2018) 205–211

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Transient epileptic and global amnesia: Real-life differential diagnosis

Jacopo Lanzone [1], Lorenzo Ricci *,[1], Giovanni Assenza, Martina Ulivi, Vincenzo Di Lazzaro, Mario Tombini

Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico of Rome, via Álvaro del Portillo, 21, 00128 Rome, Italy

ARTICLE INFO

Article history:
Received 11 March 2018
Revised 20 July 2018
Accepted 21 July 2018
Available online xxxx

Keywords:
Transient amnesia
Epileptic amnesia
Focal seizure
Temporal lobe epilepsy
Transient global amnesia

ABSTRACT

Objective: Transient epileptic amnesia (TEA) is an underestimated condition in emergency clinical setting, where most of transient amnesic episodes tend to be classified as transient global amnesia (TGA). We designed this study to evaluate the actual frequency of TEA in a real-life scenario and to highlight the features that can help clinicians distinguishing it from TGA.

Methods: We retrospectively collected clinical data of 83 patients who accessed our emergency ward for an abrupt onset of amnesic disorder, initially interpreted as TGA. All patients underwent neurological evaluation, magnetic resonance imaging (MRI) scan, and standard 21-channel scalp electroencephalography (EEG) recording (standard EEG [st-EEG]). Moreover, patients with borderline epileptiform abnormalities on st-EEG or with normal st-EEG but high clinical suspicion for TEA underwent a 16-channel 24-hour ambulatory EEG (24-h EEG). Clinical features, neurophysiological, and neuroimaging data were analyzed and compared in the two groups (TEA and TGA).

Results: Diagnosis of TEA, according to Zeman's criteria, was made in 15 patients (18%). From a clinical point of view recurrence ($p < .001$) and atypical symptoms such as confusion or language disorder (TGA plus manifestations), appear to be key elements in order to discriminate between TEA and TGA (80% of patients with TEA vs 7.8% of patients with TGA; $p < .001$). In our sample, duration of the episodes did not significantly differ between TGA and TEA, even though it is usually described as shorter for TEA. This result could be related with a prolonged postictal state in these patients. The analysis of st-EEG results evidenced low sensitivity for interictal epileptiform abnormalities (IEAs) detection (52.3%), with not conclusive data in distinguishing TEA from TGA. On the contrary, 24-h EEG showed IEAs in all patients with epilepsy, mostly during sleep, suggesting an essential diagnostic role of long-lasting EEG recording for TEA. Finally, structural abnormalities were more frequent in patients with TEA (26.6%). In the group with TGA, the only imaging alteration found was diffusion weighted imaging (DWI) hippocampal hyperintensity.

Conclusion: Our findings show that in a real-life clinical scenario, TEA is frequent but often overlooked. However, simple clinical data and widely available neurophysiological examinations can truly help to effectively distinguish TEA from TGA.

1. Introduction

Transient amnesic syndromes are distinct clinical syndromes with impressive features, regularly encountered by neurologists in acute clinical setting. Diagnosis of these syndromes can be difficult, and their nature has been debated for over 50 years [1].

Among the typical examples of acute-onset amnesic syndromes, transient global amnesia (TGA) is without any doubt the most emblematic; TGA is characterized by the sudden onset of dramatic anterograde amnesia lasting up to 24 h. Although the etiology of this specific syndrome is unknown, there is consistent evidence that assigns a causative explanation to a transient disturbance of specific hippocampal circuits involved in memory processing [2,3].

On the other hand, transient epileptic amnesia (TEA) syndrome is an underdiagnosed clinical entity that can occasionally explain an ictal amnesic disorder [4]; it can be attributable to focal ictal or interictal epileptic discharges, usually within the temporal lobe. The relationship between epilepsy and amnesic disorders has been suspected for over a century, but it was Kapur who first came up with the term TEA in 1993, giving its own dignity to this amnesic syndrome. They described TEA as a clinical entity similar to TGA, distinguished by its brevity and recurrence [5]. It is common knowledge that epilepsy can manifest itself with pure amnesic disorder [6], presenting slight to none typical epileptic manifestations (focal seizures with impaired awareness, focal to secondarily generalized seizures, epileptic aura, etc.), and it is especially now well-known that temporal lobe involvement may influence performance in memory-related tasks [7]. Nevertheless, since the definition

* Corresponding author.
E-mail addresses: ricci.lorenzo90@gmail.com (L. Ricci), m.tombini@unicampus.it (M. Tombini).
[1] The authors equally contributed to the paper.

https://doi.org/10.1016/j.yebeh.2018.07.015
1525-5050/

given by Kapur [5], TEA has struggled to impose its-self as a well-recognized epileptic syndrome, mainly for its subtle manifestations, its overlap with temporal lobe epilepsy (TLE) and the similarity with TGA.

This disease appears to present more frequently in the adult life, with a slight predominance in male patients [8]; it happens preferentially upon awakening and tends to recur [9]. In 1998, Zeman et al. proposed the following diagnostic criteria for TEA [10]: (1) a history of recurrent witnessed episodes of transient amnesia; (2) cognitive functions other than memory judged to be intact during typical episodes by a reliable witness; (3) evidence for a diagnosis of epilepsy on the basis of one or more defined characteristics (epileptiform abnormalities on electroencephalography, the concurrent onset of other clinical features of epilepsy such as lip-smacking or olfactory hallucinations, a clearcut response to anticonvulsant therapy). Evidences of this syndrome as described by Zeman et al. [10] can easily pass unrecognized. The majority of patients present negative or nonspecific scalp EEG; the rate of clear epileptiform abnormalities in EEG is reportedly 37% [9]; thus, the high rates of EEG normality often lead to a misdiagnosis in the emergency room, and sometimes even in the neurological ward leading TEA to being mistaken for TGA [11]. It is noteworthy to say that some studies demonstrated how high density EEG could enhance the accuracy in the diagnosis [12]; however, this technique is time- and cost-consuming, and it is not currently included in the common diagnostic work-up for ictal amnesic disorders.

The difficulty in making a diagnosis on the basis of Zeman's criteria has been evidenced by Ukai and Watanabe [13], who proposed a new classification for this spectrum of disease: according to these authors patients who meet all of the criteria of Zeman et al. [10] should be regarded as having TEA, while patients who do not experience amnesic attacks despite suffering from accelerated long-term forgetting (ALF) [14,15] and/or autobiographical amnesia could be considered to be suffering from 'broad TEA'; nevertheless in patients with atypical cognitive impairment and epileptic alterations on scalp EEG an epileptic etiology could be considered even if they never reported ictal amnesia and a TEA like disorder.

Finally, it was recently proposed [16] that TEA could be a peculiar form of TLE with specific involvement of circuits deputed to the functioning of declarative memory; however, the borders of TEA still somehow remain still somehow blurred, and its potential overlap with late onset epileptic amnesia and cognitive disorders related to long-standing epilepsy such as temporal mesial sclerosis must be considered [17,18].

The aim of our study was to evaluate the accuracy of diagnosis of TEA and TGA in a real medical practice scenario and to identify the main features differentiating the two disorders. To this purpose, we retrospectively analyzed all clinical and instrumental features of patients who came to our attention for an abrupt occurrence of amnesic disorder that first was diagnosed as TGA; then, we identified those patients who met Zeman's criteria for TEA and thus suffered from epilepsy rather than TGA. In this way, we divided our population into groups with TEA and TGA, and we investigated whether there are distinctive features that can help clinicians to differentiate TEA from TGA with greater sensitivity. We regard this matter of critical relevance because patients with TEA tend to promptly answer to therapy with antiepileptic drugs (AEDs), and a high rate of misdiagnosis means that many among these patients have to cope with recurrent amnesic episodes without a proper pharmacological treatment.

2. Patients and methods

2.1. Study population

For the purpose of the study, we retrospectively analyzed files and information regarding all patients, who were referred to our second level facility from a first level emergency department (ED) from 2010 to 2018 because of one or more episodes of transient amnesia that required admission in the ED. The exclusion criteria were as follows: psychiatric comorbidities, dementia, and diagnosis of secondary cause for acute amnestic syndrome (transient ischemic attack, metabolic encephalopathy, intoxication, psychogenic fugue, dissociative disorders, hypoglycemia) (Fig. 1). Thus, we identified 91 patients admitted for a sudden onset amnesic disorder of which 8 patients were excluded since they met exclusion criteria (1 mild ischemic stroke, 4 patients with confusion in the context of dementia, 2 patients with psychiatric comorbidities, 1 patient with hepatic encephalopathy). Finally, we identified 83 patients who matched the established criteria. All patients were admitted in our ward within 24 h from the symptoms onset. At first evaluation in ED, all 83 patients were diagnosed as TGA on the basis of clinical history collected by ED medical doctors and first level examinations (routine blood tests, electrocardiogram [EKG], and brain computed tomography [CT] scan) (Fig. 1). Thus, for all patients clinical characteristics of attacks, context of occurrence, possible triggering factors, and cognitive problems were assessed by experienced neurologists with the aid of witnesses if available. We gave particular attention in asking for the following: duration of the event, recurrence, happening upon awakening, and presence of symptoms that are not typical for TGA (staring, automatisms, olfactory hallucinations, language disorder, tremor, ataxia, spatial disorientation, severe confusion as reported in the clinical records, transient facial palsy, etc.); from now on, we will refer to such symptoms as 'TGA plus'. The term confusion, even if we are accustomed to its use in clinical practice, can be misleading; we specify that in this paper we use it with the meaning of severe attention impairment. All patients underwent a full neurological examination and waking standard electroencephalography (EEG) (st-EEG) recording with 21-channel scalp EEG system (international 10–20 system, sampling rate 256 Hz, 0.3-Hz to 70-Hz band pass filter; Micromed Brain Quick System). The EEG recording was performed in the laboratory in eyes closed, resting condition, for the duration of 10–15 min including hyperventilation and intermittent photic stimulation. Moreover, patients with borderline epileptiform abnormalities on st-EEG or with normal st-EEG but high clinical suspicion for TEA underwent 16-channel 24-hour ambulatory EEG (24-h EEG, sampling rate 256 Hz, 0.3-Hz to 70-Hz band pass filter; Micromed Brain Spy System), which allowed us to record even nocturnal sleep in all subjects studied. For the purpose of this study, we considered EEG to be abnormal if focal or diffuse interictal epileptiform transients (spike, sharp wave, or spike-and-wave discharges) or focal theta waves with spiky morphology were found. Finally, all patients performed cerebral MRI (1.5-T MRI, T1, T2, DWI, apparent diffusion coefficient (ADC), fluid attenuation inversion recovery (FLAIR) brain sequences). Moreover, due to the retrospective nature of the study although some of the patients with TEA complained mild memory impairment, neuropsychological evaluation was not performed since it was not part of our routine work-up.

According to Zeman's criteria [10] evidence of epilepsy was supported through any combination of epileptiform interictal abnormalities on EEG, reports of simultaneous classically epileptic features ('TGA plus' symptoms), and/or a positive treatment response to antiepileptic drugs (AEDs). Thus, 15 patients out of 83 (18%) resulted as affected by focal epilepsy and were diagnosed as TEA; their features were summarized in the Table 1. In detail, all patients fulfilled at least 2 supportive criteria as specified at point 3 of the Zeman's criteria: 10 out of 15 patients had all 3 criteria (epileptiform abnormalities, 'TGA plus' symptoms and clearcut response to anticonvulsant therapy), 2 out of 15 had epileptiform abnormalities and 'TGA plus' symptoms (their outcome was not known as they were lost at follow-up) and 3 out of 15 patients had epileptiform abnormalities and clearcut response to anticonvulsant therapy (they were all seizure-free). Differences in demographics, clinical features, and on investigation findings were compared in patients with TGA and TEA in order to highlight distinguishing characteristics between the two groups (Table 2). Our study was approved by local Ethics Committee.