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EPILEPSY SYNDROMES IN DEVELOPMENT

Transient epileptic amnesia: An emerging late-onset epileptic syndrome

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Summary

Transient epileptic amnesia (TEA) is a distinct neurologic condition occurring in late-middle/old age and presenting with amnesic attacks of epileptic nature and interictal memory disturbances. For many years this condition has been associated with the nonepileptic condition of transient global amnesia (TGA) and still today is poorly recognized by clinicians. Despite the clinical and laboratory findings that distinguish TEA from TGA, differential diagnosis may be difficult in the individual patient. Every effort must be employed for an early diagnosis, since antiepileptic treatment may readily control both ictal episodes and memory disturbances.

KEY WORDS: Transient epileptic amnesia, Amnesia, Transient global amnesia.

Historical Background: Transient Global Amnesia and Transient Amnesia of Epileptic Origin

The possibility that episodes of transient and isolated amnesia might have an epileptic origin has been recognized for more than 100 years (Hughlings-Jackson, 1889). These epileptic attacks have been generally overlooked and poorly defined in the literature, being often confused with the more widely known syndrome of transient global amnesia (TGA).

Fisher and Adams (1964) first used the term TGA to define the clinical picture of pure transient amnesia, characterized by the abrupt onset of severe anterograde amnesia, with general cognition and behavior appearing normal in other respects and neurologic status being otherwise normal. Retrograde amnesia is often present in this situation but is of variable duration, ranging from a few hours up to years. Patients remain fully communicative and alert and often carry out complex tasks; however, they are often agitated or anxious, and may repeat the same questions every few minutes. After resolution of the attack there is a rapid return of anterograde memory; however, since patients had not been able to lay down new memories during the attack, they will never be able to recall the episode itself. Caplan (1985) proposed to reserve the definition of TGA for cases of attacks of well-defined amnesia without disturbance of consciousness, focal neurologic symptoms, or epileptic features in patients who do not have active epilepsy, in whom the amnesic disturbance is transient, usually lasting up to 24 h. Accordingly, cases of transient pure amnesia of demonstrated epileptic origin should not be defined as TGA. However, even after 1985, the term TGA was still employed (Tassinari et al., 1991; Meo et al., 1995) in describing case reports of amnesic attacks that were quite similar to "classic" TGA from a clinical standpoint but that had a clear epileptic pathogenesis, demonstrated by electroencephalography (EEG) findings and/or response to antiepileptic treatment. In many of these reports, however, the attacks of "epileptic TGA" also had some peculiar clinical features that distinguished them from typical TGA cases, in particular the tendency to recur and the duration of the attacks which, while being considerably longer than typical epileptic seizures, did, however, usually last no longer than 1 h. Further confusion regarding this issue was added by several case reports describing shorter attacks (lasting about 10 min) in which amnesia was not an isolated symptom but was preceded by typical epileptic ictal phenomena such as clouding of consciousness and/or motor automatisms, which were defined by the authors as epileptic amnesic attacks (Pritchard et al.,

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1985; Gallassi et al., 1992). Both the longer attacks with isolated amnesic features and the shorter ones accompanied by other ictal phenomena shared the same epileptic pathogenesis, but while the former resembled the clinical picture of TGA, the latter were clearly distinguishable and had evident epileptic features. However, because both were epileptic seizures strongly characterized by amnesic disturbances, the use of a different terminology in their description was surely inappropriate and of poor help for the clinician. Similarly, the denomination of ''TGA of epileptic origin'' for the former seems to be a misnomer, since the exclusion of epilepsy had been recognized as one of the diagnostic criteria for defining TGA.

The Concept of Transient Epileptic Amnesia: A New Epileptic Syndrome in the Elderly?

Kapur reviewed several cases of amnesia associated with epilepsy, proposing the definition of transient epileptic amnesia (TEA) for this condition (Kapur, 1993). The author remarked that TEA was a distinct neurologic condition, quite frequent but poorly recognized both by clinicians and researchers, and underlined the distinctive clinical features that distinguished TEA from TGA. More recently, Butler published an impressive series of patients with TEA with a detailed clinical and EEG study (Butler et al., 2007). This report confirms that both longer, purely amnesic seizures and short amnesic attacks with additional ictal symptoms can occur in the same patient, suggesting a common pathogenesis of both episodes. Patients with TEA presented in this series show a consistent clinical picture, with age of onset, natural history, and interictal disturbances being remarkably similar in most cases: TEA begins in late-middle to old age and is responsive to relatively low doses of anticonvulsant medication, but many patients report persistent interictal memory disturbances, consisting of accelerated long-term forgetting and autobiographic amnesia. The possible relationship of these disturbances with uncontrolled seizures has been suggested, and interictal memory disturbances have been consequently considered as a phenomenon related to ictal or subclinical epileptiform activity arising from the temporal lobes (Kapur, 1993; Gallassi, 2006). However, there are also reports in which memory disturbances persist and/or worsen despite good seizure control and low doses of anticonvulsants (Butler et al., 2007).

Because of its frequency and to its consistent clinical picture, Butler proposes TEA as a distinctive epilepsy syndrome to be considered for inclusion in a classification of epilepsies and epileptic syndromes (Butler et al., 2007). An epileptic syndrome with the same ictal and interictal features had been previously described by Gallassi et al. (1992) and Gallassi (2006) as epileptic amnesic syndrome. However, the term TEA is probably more appropriate, since it highlights the similarity of this syndrome to TGA but also its distinction from this condition (Zeman et al., 1998).

Diagnostic Criteria and Differential Diagnosis of TEA versus TGA

Pure amnesic ictal episodes of epileptic origin do actually exist and when recurrent give rise to a distinctive epileptic syndrome that most authors define as TEA. The episodes of TEA share several clinical similarities with, but also have many differences from, the nonepileptic episodes of TGA. Some of the peculiar features of TEA are strictly dependent on its epileptic nature, and, when present, usually do clearly suggest the correct diagnosis to the clinician: the presence of interictal EEG epileptiform abnormalities, other ictal symptoms during or immediately preceding the amnesic episode, different seizure types independent from the amnesic episodes, and the reduction or cessation of the episodes after the introduction of antiepileptic treatment. Other features are not specifically suggestive of epilepsy, but have been reported as typical of TEA (Kapur, 1993; Butler et al., 2007) and must be kept in mind when evaluating a patient with transient amnesia of an unexplained etiology. In particular, TEA attacks often occur on awakening, whereas TGA episodes are often triggered by emotional or physical stress. Retrograde amnesia in TEA is often more severe than anterograde amnesia, and in some cases may be the sole amnesic disturbance; as a consequence of the incomplete anterograde amnesia, many patients with TEA may have a partial memory of the amnesic episode, reporting that they ''were not able to remember.'' In contrast, patients with TGA have both retrograde and anterograde amnesia and do not preserve any memory of the episode after its resolution. As a consequence of the partial rather than global anterograde amnesia, TEA is also often characterized by an absence of the repetitive questioning and anxiety that is typical of patients with TGA, who ask again and again the same question and rapidly forget the answer. TEA episodes tend to be shorter than TGA, usually lasting <1 h in contrast with TGA, which has an average duration of 4–6 h. Finally, TEA episodes tend to recur in contrast with the low recurrence rate of TGA (Zeman et al., 1998; Butler et al., 2007).

At the present, a diagnosis of TEA can be proposed in the presence of: (1) 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 based on one or more of the following: epileptiform abnormalities on the EEG, the concurrent onset of other

features of epilepsy (such as lip-smacking and olfactory hallucinations), and clear-cut response to antiepileptic treatment (Zeman et al., 1998).

The diagnostic assessment of a patient presenting with an acute episode of pure amnesia is not always simple, and, in particular, at the onset of such manifestations, the differential diagnosis between TEA and TGA may be difficult. Recurrence of attacks and response to antiepileptic treatment cannot be predicted when observing the first attack. TEA attacks have usually a shorter duration, but this is not always the case, since up to 30% of patients in the series from Butler et al. experience episodes lasting more than 1 h (Butler et al., 2007). Additional ictal manifestations may be lacking or unnoticed; finally, the absence of interictal EEG abnormalities does not exclude the possibility of TEA, since EEG may be unrevealing in up to two-thirds of the patients (Butler et al., 2007), possibly due to the fact that epileptogenic areas in these cases are located in deep temporal structures, the interictal epileptiform activity of which may not be evident in routine EEG studies (Table 1).

Obtaining an EEG during the amnesic episode can be of great help in distinguishing between TEA and TGA. Despite the great number of cases of TEA reported in the literature, few descriptions of EEG recordings during the TEA episode are reported (Tassinari et al., 1991; Gallassi et al., 1992; Lee et al., 1992; Palmini et al., 1992; Meo et al., 1995; Vuilleumier et al., 1996; Maheu et al., 2004; Butler et al., 2007). In several of these reports, when an actual amnestic episode was captured with an ictal EEG

Table 1. Differential diagnosis between transient global amnesia (TGA) and transient epileptic amnesia (TEA)

	TGA	TEA	Comments
Duration of attacks	1–24 h	<1 h	Up to 30% of TEA episodes last longer than 1 h
Interictal EEG	No epileptiform abnormalities	Epileptiform abnormalities on temporal or fronto-temporal regions	Up to 70% of cases of TEA have normal interictal EEG
Other ictal symptoms (accompanying the amnesic attack, or occurring independently)	No	Yes	Up to 30% of cases of TEA have only pure amnesic attacks; additional minor ictal phenomena may be unnoticed
Recurrence of attacks	Rare	Frequent	–
Response to antiepileptic treatment	Absent	Common	–

EEG, electroencephalography.

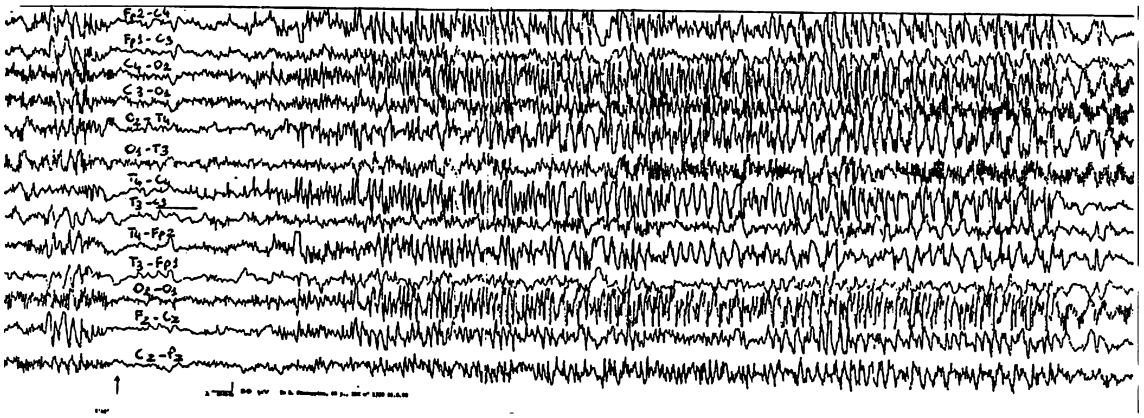

Figure 1.
Ictal electroencephalography (EEG) during an amnesic episode of epileptic origin in a patient with transient epileptic amnesia (TEA). Discharge beginning with diffuse fast low-amplitude activity (↑) followed by small spikes on the right temporocentral areas(→) and successively by a recruiting rhythm on the right hemisphere spreading on the left side.
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recording (Lee et al., 1992; Meo et al., 1995; Vuilleumier et al., 1996) nonconvulsive status epilepticus was detected (Fig. 1). The remaining reports of EEG performed during a TEA episode, however, reveal the amnesic episode as a postictal phenomenon (Tassinari et al., 1991; Gallassi et al., 1992; Palmini et al., 1992; Maheu et al., 2004; Butler et al., 2007). Incidentally, this latter possibility seems to occur more frequently when amnesic episodes are short lasting and heralded by other ictal manifestations (Tassinari et al., 1991; Gallassi et al., 1992; Butler et al., 2007) or when they are prolonged postictal states following a cluster of repetitive seizures (Palmini et al., 1992; Maheu et al., 2004).

Obviously misdiagnosis of TEA is not inconsequential. Misdiagnosis may delay antiepileptic treatment and possibly worsen interictal memory disturbances. Overdiagnosis, on the other hand, might lead to unnecessary medication with anticonvulsants, which is potentially detrimental, especially in elderly patients. Efforts should be made to obtain ictal EEG; in interictal EEG studies, sleep deprivation has shown to be of help in activating epileptiform abnormalities, which are often absent in basal EEG (Butler et al., 2007).

Further work is warranted to clarify if ictal and postictal amnesic states are actually part of the same condition and to understand the mechanisms underlying interictal memory disturbances. Clarification of these issues is necessary before considering TEA as a distinctive epileptic syndrome.

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We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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