The Syndrome of Transient Epileptic Amnesia

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Objective: Transient amnesia can be the principal manifestation of epilepsy. This diagnosis, however, is seldom suspected by clinicians and remains controversial. The amnestic attacks are often associated with persistent memory complaints. This study was designed to provide the first description of transient epileptic amnesia in a substantial series of patients.
Methods: Fifty patients were recruited over 18 months using the following diagnostic criteria: (1) recurrent, witnessed episodes of amnesia; (2) other cognitive functions intact during attacks; and (3) compelling evidence of epilepsy. We assessed clinical features and performed neuropsychological evaluation in cases and 24 matched control subjects.
Results: Transient epileptic amnesia develops in later life (mean onset, 62 years). Amnestic episodes are frequent (median, 12/year), brief (median duration, 30 –60 minutes), and often occur on waking (37/50 cases). Epilepsy was the initial specialist diagnosis in only 12 of 50 cases. Attacks ceased on anticonvulsant medication in 44 of 47 treated patients. A total of 40 of 50 cases described persistent memory difficulties. Despite normal performance on standard memory tests, patients exhibited accelerated forgetting of verbal and visual material over 3 weeks by comparison with matched control subjects (p 0.001). They also showed loss of autobiographical memories for events extending back over 40 years (p 0.05).
Interpretation: We propose that transient epileptic amnesia is a distinctive epilepsy syndrome, typically misdiagnosed at presentation and associated with accelerated long-term forgetting and autobiographical amnesia. The syndrome is of clinical and theoretic importance.

Transient amnesia is an arresting clinical phenomenon. While other cognitive functions remain intact, the sufferer is temporarily unable to form new memories (anterograde amnesia), to retrieve established memories (retrograde amnesia), or both. Recognized causes include transient global amnesia (TGA), closed head injury, psychogenic amnesia, transient ischemic attacks, migraine, and drug effects. [1]

Several authors since Hughlings-Jackson [2] have proposed that episodes of transient amnesia can be a manifestation, sometimes the sole manifestation, of epilepsy.[3–9] Single case reports and small series indicate that transient epileptic amnesia (TEA) is characterized by brief (less than 30 minutes), recurrent attacks of amnesia in middle-aged or elderly subjects, often occurring on waking. In addition, patients with TEA frequently report two varieties of persistent, interictal memory disturbance that are invisible to standard neuropsychological tests: (1) the accelerated forgetting, over days or weeks, of newly acquired information [10]; and (2) a patchy but dense loss of memories for salient autobiographical events in the more remote past. [10,11] These phenomena may help to explain the well-documented, but poorly understood, memory difficulties reported by more than 50% of people with epilepsy [12] and pose challenges for standard theories of memory. TEA is therefore both clinically and theoretically important.

We describe the clinical, electrophysiological, neuroimaging, and neuropsychological characteristics of 50 patients with TEA, documenting the phenomena of accelerated forgetting and autobiographical amnesia. The diagnosis of epilepsy was considered initially in only 12 of these patients, demonstrating that this manifestation of epilepsy is underrecognized.

Subjects and Methods

Fifty cases of TEA (incident or established) were recruited to the TIME (The Impairment of Memory in Epilepsy) Study

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from the Cognitive Disorders Clinics at the Western General Hospital, Edinburgh, and at Addenbrooke's Hospital, Cambridge, and via the British Neurological Surveillance Unit (a service of the Association of British Neurologists), using Zeman and colleagues' [9] diagnostic criteria: (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; and (3) evidence for a diagnosis of epilepsy based on one or more of the following: epileptiform abnormalities on electroencephalography (EEG), the concurrent onset of other clinical features of epilepsy (eg, lip-smacking, olfactory hallucinations), a clear-cut response to anticonvulsant therapy.

The study was approved by the Multicentre Research Ethics Committee, United Kingdom (MREC 03/10/77). All participants gave written, informed consent.

Clinical Characteristics of Transient Epileptic Amnesia

One investigator (C.R.B.) conducted all interviews. In each case, a detailed history was obtained from the patient and at least one witness. A standard pro forma was used to collect data on demographics, clinical features of the amnestic attacks, other transient neurological or cognitive symptoms, interictal memory complaints, risk factors for epilepsy and cerebrovascular disease, and medical and psychiatric history. Major depression, generalized anxiety disorder, and panic disorder subsections of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [13] were administered. A neurological examination was performed. Medical case notes and correspondence were reviewed.

EEG was performed in 49 cases and reviewed by the consultant neurophysiologist at the referring center. Results were classified as: (1) normal or as showing (2) nonspecific or (3) clear, recurrent epileptiform abnormalities.

Magnetic resonance imaging was performed on a 1.5-Tesla GE Signa LX scanner (GE Medical Systems, Milwaukee, WI) at the SFC Brain Imaging Centre for Scotland, Western General Hospital, Edinburgh, or on a scanner of the same model at the MRIS Unit, Addenbrooke's Hospital, Cambridge. All scans (T1- and T2-weighted, fluid-attenuated inversion recovery, gradient-echo, and diffusion-weighted sequences) were reviewed for clinical abnormalities by an experienced neuroradiologist (J.M.W.).

Neuropsychological Profile

Standard neuropsychological tests were used to assess general intelligence (Wechsler Abbreviated Scale of Intelligence [14]), anterograde memory (immediate and 30-minute delayed recall of a prose passage; from Wechsler Memory Scale-III [15], copy and 30-minute delayed recall of the Rey–Osterreith complex figure, [16] the Recognition Memory Test [17]), memory for famous faces (Graded Faces Test [18]), language (Graded Naming Test [19]), and executive function (letter and category fluency, Wisconsin Card Sorting Test—64 Card Version [20]).

Accelerated Forgetting

Learning and long-term retention were then examined in a subset of 24 TEA patients and 24 pairwise matched control subjects (see later). Patients were selected for their normal performance on standard anterograde memory tests, lack of other evident cognitive deficits or psychiatric diagnoses, and geographical proximity to the study center. Of these 24 patients, 12 had subjective complaints of accelerated forgetting. A list of 15 words (from the Rey Auditory Verbal Learning Task[21]) was presented orally over a minimum of 5 and a maximum of 15 trials until the subject attained 90% accuracy at free recall. Recall of the words was then tested at delays of 30 minutes, 1 week, and 3 weeks. A similar procedure was used for reproduction of seven visually presented designs (from the Graham–Kendall Memory for Designs test[22]). Subjects were not forewarned about the 1- and 3-week probes, but they were explicitly requested not to rehearse the material. Two equivalent versions of each test were available so that cohabitants did not receive the same material. Patients were asked to record any seizures or auras experienced between testing sessions.

Remote Memory

A semistructured interview (the Modified Autobiographical Memory Interview; see supplementary material) was used to assess memory for autobiographical facts and events relating to two topics for each decade of the subject's life. For each topic (eg, "holiday"), subjects were asked to answer five questions designed to probe semantic, or factual, memory (eg, "How long did you stay?") and produce one detailed episodic memory (eg, "Can you recall any incident, even if small, that occurred during your holiday in Seton Sands?"). Episodic memories were scored out of 5 according to their degree of specificity and experiential detail, based on the scheme that Graham and Hodges [23] described. A witness, usually a spouse, was always present to corroborate the subject's account.

Control Subjects

Seventeen age- and education-matched, neurologically normal control subjects were recruited by asking patients from the accelerated forgetting subset to nominate a volunteer (usually a spouse or close friend). Seven patients were unable to nominate their own control subjects; for these patients, a similarly matched control subject was obtained from the volunteer panel of the Medical Research Council Cognition and Brain Sciences Unit at the University of Cambridge. Control subjects underwent a medical history interview, magnetic resonance scanning, and received the standard neuropsychological, accelerated forgetting, and autobiographical memory test batteries.

Statistical Analysis

The performance of TEA patients on standard neuropsychological testing was compared with that of control subjects using independent sample t tests or the Mann–Whitney U test where appropriate. To compare long-term forgetting rates of the patient and control groups, we conducted repeated-measures analyses of variance (ANOVA), with factors of participant group and delay (30 minutes, 1 week, and 3 weeks), using recall score as the dependent variable. The Greenhouse–Geisser correction for nonsphericity was applied where necessary. Semantic and episodic memory scores on

the Modified Autobiographical Memory Interview were obtained for each subject across the five most recent life decades and were analyzed using repeated-measures ANOVA, with factors of participant group and decade (most recent (Z), Z-1, Z-2, Z-3, Z-4). Planned independent sample *t* tests were used to explore the temporal extent of identified differences. All analyses were performed using SPSS for Windows version 13 (SPSS, Chicago, IL).

Results

A total of 50 patients (34 male patients) fulfilling the diagnostic criteria for TEA were recruited between August 2003 and April 2005. Of these, 30 were diagnosed and referred during the study period, 10 already carried the diagnosis and were referred from other hospitals, and 10 had been previously diagnosed at one of the 2 study centers. The distribution of patients meeting each of the three diagnostic criteria for epilepsy used in this study is shown in Table 1 and Figure 1. Mean age at the onset of amnestic attacks was 62.1 years (standard deviation [SD] 9.1; range, 44 –77 years), and at entry into the study was 68.3 years (SD 8.6; range, 46– 84 years). Mean duration of education was 12.2 years (SD 2.9). Twenty-four pairwise matched control subjects (mean age, 67.7 years [SD 8.2; range, 49– 81 years]; mean duration of education, 12.5 years [SD 3.1]; 10 male subjects) were recruited.

All patients were referred to the TIME Study with a diagnosis of epilepsy. Initially, however, the following diagnoses had been entertained by the physician: unspecified (26%), temporal lobe epilepsy (24%), TGA (20%), "psychogenic" (18%), transient cerebral ischemia/stroke (6%), cardiac arrhythmia (4%), dementia (2%). The median delay to the diagnosis of TEA was 12 months (mean, 21 months; interquartile range [IQR], 5–25).

The clinical features are summarized in Table 2. A median total number of 10 amnestic attacks (IQR, 6–30) was experienced over a median (first to last seizure) of 17.5 months (IQR, 6–56) at a median frequency of 12 attacks per year (IQR, 5–20). Attacks occurred on waking in 37 patients (74%), exclusively so in 11 of these patients (22%). No other consistent triggers were identified. Ten patients (20%) described experiencing nonspecific symptoms, such as "a floaty feeling" or nausea, before the amnesia. Attack onset was sudden and heralded by questions betraying a loss of memory such as "Where am I?" "What are we doing here?" or "What day is it?" Twenty-five patients (50%) typically exhibited repetitive questioning. Execution of complex, purposeful actions (see Appendix and supplementary materials for examples), together with appropriate responses in conversation, were taken to indicate preservation of nonmemory cognitive functions during the attack. Anterograde amnesia was often incomplete, with 28 patients (56%) reporting at least partial recall of their attacks. The median duration of the amnestic attacks was "30 to 60 minutes" (range, "less than 1 minute" to "days"), and 70% of patients typically experienced episodes lasting less than 1 hour.

Amnesia was the sole feature of all attacks in 14 patients (28%), and 46 patients (92%) experienced at least one such episode. However, certain other features sometimes preceded or accompanied the amnesia: olfactory or gustatory hallucinations (42%); automatisms such as chewing, lip-smacking, or fiddling with clothing (36%); and brief episodes of unresponsiveness (24%). Two patients suffered temporally distinct, generalized tonic-clonic seizures.

Reports of persistent memory difficulties were common. Thirty-five patients (70%) described a patchy loss of remote autobiographical memories. In 29 of these patients (83%), some of the "lost memories" had been acquired before the clinical onset of epilepsy, sometimes several decades before. Twenty-two patients (44%) reported problems with "holding on to a memory for more than a few days," suggesting the presence of accelerated forgetting. Eighteen patients (36%) had developed significant navigational difficulties.

A history of psychiatric disease was present in 12 patients (24%) and 5 control subjects (21%). Histories included current major depression (two patients), previous depression (nine patients, four control subjects), past anxiety (one patient), and past panic disorder (one control subject). No patient or control subject had a history of medically unexplained symptoms. "Pathological emotionalism", usually inappropriate crying, was described by nine patients (18%) and no control subjects. Eleven patients (22%) and five control subjects (21%) had experienced migraine at some time. Birth trauma, febrile seizures, head injury, intracranial infection, and family history of epilepsy were minimally represented in patient and control groups. There was no excess of overt cardiovascular or cerebrovascular disease in the patient group. A history of alcohol consumption in excess of recommended levels (21 units/wk for men, 14 units/wk for women) was present in 12 patients (24%) and 4 control subjects (17%). Neurological examination did not demonstrate any major or consistent abnormalities.

A total of 49 patients (98%) had undergone EEG. Clear, recurrent epileptiform abnormalities were present in 18 (37%) patients (although only after sleep deprivation in 8 patients) and were consistently over temporal or frontotemporal regions. Eight were left-sided, six were right-sided, and four were bilateral. Sixteen patients (32%) had nonspecific, focal slow-wave changes, and no abnormality was detected in 15 patients (31%). A total of 47 patients had MRI of the brain, and 2 further patients had computerized tomography. Only one patient, whose clinical syndrome was indistinguishable from the rest of the group, had a ma-

Table 1. Clinical Characteristics Pertaining to the Diagnosis of all 50 Transient Epileptic Amnesia Patients

Identification No.	Sex	Age at Onset (yr)	Total Number of Amnestic Attacks	First to Last Attack (mo)	Duration of Attacks	Amnesia on Waking	Number of Criteria Met	EEG	Other Features Sometimes Present	Treatment Response
11	F	57	5	4	5–15 minutes	Yes	3	Epil	Autom	Com
56	F	49	5	72	2–24 hours	Yes	3	Epil	Olf hall	Com
112	M	54	6	12	30 minutes to 1 hour	Yes	3	Epil	Autom/unresp	Com
37	M	61	6	2	15–30 minutes	Yes	3	Epil	Olf hall/autom/ CPS	Com
49	F	69	15	24	2–24 hours	Exclusively	3	Epil	Olf hall/autom/ GTC	Com
31	F	57	15	17	<1 minute		3	Epil	Olf hall/unresp	Com
83	M	72	18	21	15–30 minutes	Yes	3	Epil	Olf hall/autom	Com
42	F	70	50	86	2–24 hours	Exclusively	3	Epil	GTC	Partial
8	F	67	50	18	5–15 minutes	Yes	3	Epil	Olf hall	Com
21	M	53	60	156	2–24 hours	Yes	3	Epil	Olf hall	Com
12	F	63	2	5	30 minutes to 1 hour	Exclusively	2		Olf hall	Com
61	M	71	2	3	2–24 hours	Exclusively	2		Olf hall	Com
22	M	58	3	3	30 minutes to 1 hour	Exclusively	2		Olf hall	Com
116	M	44	3	283	4 days		2	Epil	(pure amnesia)	Com
40	M	65	4	12	2–24 hours	Yes	2		CPS	Com
64	M	60	4	6	5–15 minutes		2		Olf hall	Com
94	M	69	5	4	30 minutes to 1 hour	Yes	2		Autom	Com
38	F	45	5	7	15–30 minutes	Yes	2		Olf hall	Com
93	M	60	6	6	2–24 hours	Yes	2		Autom/unresp	Com
95	F	52	6	168	2–24 hours	Yes	2	Epil	(pure amnesia)	Com
55	M	59	7	6	30 minutes to 1 hour		2		Olf hall/autom	Com
3	M	70	8	4	15–30 minutes		2		Autom/unresp	Com
62	M	56	8	16	30 minutes to 1 hour	Exclusively	2		Olf hall	Com
50	M	77	10	27	2 days	Yes	2		Autom	Com
68	M	68	10	12	15–30 minutes		2		Olf hall	Com
88	M	49	10	4	15–30 minutes	Exclusively	2	Epil	(pure amnesia)	Com
13	M	75	12	16	15–30 minutes	Yes	2		Olf hall	Com
91	M	69	15	18	15–30 minutes	Yes	2	Epil	Autom/unresp	Not treated
36	M	76	16	9	15–30 minutes	Exclusively	2		Olf hall	Com
69	M	59	16	5	15–30 minutes	Yes	2		Unresp	Com

Table 1. Continued

Identification No.	Sex	Age at Onset (yr)	Total Number of Amnestic Attacks	First to Last Attack (mo)	Duration of Attacks	Amnesia on Waking	Number of Criteria Met	EEG	Other Features Sometimes Present	Treatment Response
32	M	71	19	7	15–30 minutes		2		Autom	Com
9	M	52	20	24	15–30 minutes	Yes	2		Autom/unresp	Com
114	F	61	25	65	2–24 hours	Yes	2		Autom/unresp	Com
39	F	50	30	67	5–15 minutes		2		Autom/unresp	Com
82	M	65	30	33	15–30 minutes	Yes	2		Olf hall/autom	Com
47	M	60	30	72	2–24 hours		2		Olf hall/unresp	Com
138	F	59	30	130	2–24 hours	Yes	2	Epil	(pure amnesia)	Com
10	F	66	36	25	15–30 minutes	Yes	2	Epil	(pure amnesia)	Com
90	M	60	50	40	30 minutes to 1 hour	Exclusively	2		Olf hall	Com
100	M	48	50	55	30 minutes to 1 hour	Yes	2		Olf hall/autom	Com
16	F	74	60	60	30 minutes to 1 hour		2		Autom	Partial
124	F	52	60	144	15–30 minutes		2	Epil	(pure amnesia)	Com
73	M	71	3	9	30 minutes to 1 hour	Yes	1	Epil	(pure amnesia)	Not treated
35	M	75	6	59	15–30 minutes	Yes	1		(pure amnesia)	Com
41	F	65	6	9	1–2 hours		1		(pure amnesia)	Com
51	M	49	6	9	15–30 minutes	Yes	1		(pure amnesia)	Com
92	M	73	6	6	1–2 hours	Yes	1		(pure amnesia)	Com
103	M	71	7	20	15–30 minutes		1		(pure amnesia)	Com
25	M	75	15	46	30 minutes to 1 hour	Exclusively	1		(pure amnesia)	Com
28	M	55	28	21	5–15 minutes	Exclusively	1		(pure amnesia)	Com

EEG = electroencephalogram; Epil = clear-cut epileptiform features; autom = automatisms; com = complete cessation of attacks; olf hall = olfactory hallucinations; unresp = brief period of unresponsiveness; CPS = complex partial seizures; GTC = generalized tonic-clinic seizures.

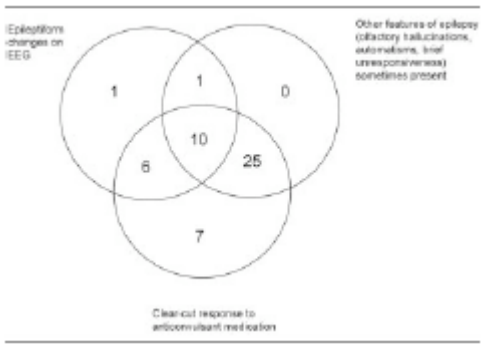

Fig 1. Venn diagram showing the distribution of patients meeting the three diagnostic criteria for epilepsy used in this study. EEG electroencephalogram.

ory (delayed recall and recognition of a story, delayed recall of the Rey–Osterreith complex figure, face and word recognition memory) and the depression rating of the Hospital Anxiety and Depression (HAD) scale. HAD depression ratings did not correlate with scores on standard memory tests (delayed recall of Logical Memory story [p 0.968] or Rey figure [p 0.962]), and there was no significant difference in depression ratings between patients with and without self-reported interictal accelerated forgetting (p 0.77) or remote autobiographical memory loss (p 0.60).

Accelerated Forgetting

Patients' and control subjects' performance on learning and delayed recall of the word list and designs is shown in Figure 2. Mann–Whitney U tests demonstrated no significant differences between patient and control groups in the number of learning trials needed to reach the 90% criterion. At 30 minutes, patients recalled a mean of 12.6 words (84.0%) and control subjects a mean of 13.9 words (92.5%), a small but statistically significant difference (p 0.007). Between 30 minutes and 1 week there was a sharp decline in recall in the patient group by comparison with control subjects (p 0.001), with little further change between 1 and 3 weeks. Patients and control subjects were indistinguishable on 30-minute recall of designs, but there was an increasing separation between the groups at 1 and 3 weeks (p 0.04). Repeated-measures ANOVA demonstrated an interaction effect of delay with group for the word list (F [1.2, 46] 16.9; p 0.001) and designs (F [1.6, 41] 4.3; p 0.03), indicating that patients' recall was differentially poorer than that of control subjects over the 3-week delay for both verbal and visual material. Separate analyses were performed comparing control subjects with patients who did (AF) and did not (AF) have subjective complaints of accelerated forgetting. For AF patients, no delay by group interaction was found for either the word list (F [2.1, 33] 1.9; p 0.15) or the designs (F [1.67, 31] 0.27; p 0.73). For AF patients, however, there was a highly significant delay by group interaction for both words (F [2.2, 33] 19.7; p 0.001) and designs (F [1.8, 31] 21.5; p 0.001). AF and AF patients did not differ from each other on any of the standard neuropsychological measures. No patients had seizures or auras between testing sessions. Within the patient group, delayed memory performance (3-week recall) did not correlate with HAD depression scores for either the word list (p 0.94) or designs (p 0.91).

Autobiographical Memory

The Modified Autobiographical Memory Interview was administered to 22 patients in the "accelerated forgetting" subset and 18 subjects from the control group. For the remaining individuals in each group (two patients and six control subjects), no witness was available to corroborate the accounts. Figure 3 shows the mean scores by decade of life for the two groups. Patients showed a slight but statistically significant impairment of semantic memory recall in three of the five most recent decades of life and clear impairment in episodic memory scores across the four most recent life decades. Repeated-measures ANOVA for semantic memory scores showed a main effect for group (F [1,38] 13.3; p 0.001) and for decade (F [3.1, 38] 3.3; p 0.02), but no group by decade interaction (F [3.1, 38] 0.5; p 0.67). Repeated-measures ANOVA for episodic memory scores demonstrated a main effect for group (F [1, 38] 24.4; p 0.001), but no effect for decade (F [4, 38] 1.48; p 0.21) or group by decade interaction (F [4, 38] 0.81; p 0.52). No correlation was observed between patients' lifetime autobiographical episodic memory scores and their HAD depression rating (p 0.76).

Discussion

In 1888, the British neurologist Hughlings-Jackson reported the case of Dr Z, a medical practitioner who suffered from an unusual form of temporal lobe epilepsy[2] During seizures he was capable of complex, purposeful behavior for which he was afterward amnestic, including, on one occasion, the examination and diagnosis of a patient with pneumonia. Over the past 50 years, case reports have suggested that some transient amnestic episodes may have an epileptic basis. [4–8] Hodges and Warlow, [24] in a longitudinal study of 114 cases of TGA, found that 8 patients, notable for the brevity and recurrence of their amnestic attacks, later developed complex partial seizures. Zeman and colleagues,[9] adopting Kapur's [7] term *transient epileptic amnesia* (TEA), reviewed 21 previously published and 10

Table 2. Core Clinical Features of Transient Epileptic Amnesia

Demographics	
Mean age at onset (yr)	62.1 (range, 44-77)
Sex distribution (M/F)	34/16
Amnestic attack characteristics	
Median number of attacks	10 (IQR, 6-30)
Median frequency (attacks per year)	12 (IQR, 5-20)
Median attack duration	30-60 minutes (range, <1 minute to days)
Cessation of attacks on AED	96%
Some attacks on waking	74%
Partial amnesia for attack	56%
Repetitive questioning	50%
Olfactory hallucinations	42%
Motor automatisms	36%
Brief unresponsiveness	24%
Interictal memory	
c/o autobiographical memory loss	70%
c/o AML for events before TEA	58%
c/o accelerated forgetting	44%
c/o topographical memory loss	36%
Investigations	
Interictal epileptiform EEG abnormalities	37%
Structural lesion on MRI	2%

IQR = interquartile range; AED = antiepileptic drug; c/o = complaint of; AML = autobiographical memory loss; TEA = transient epileptic amnesia; EEG = electroencephalogram; MRI = magnetic resonance imaging.

new cases and highlighted the distinctiveness of this form of epilepsy.

In the largest study of TEA to date, we report here the clinical and neuropsychological features of 50 cases. TEA typically begins in late-middle to old age. In this series, the male/female ratio was 2:1. The amnestic attacks are characterized by a mixed anterograde and retrograde amnesia, sometimes with repetitive questioning. The anterograde component, however, is often incomplete, and patients may report being able to "remember not being able to remember." Attacks commonly occur on waking, a helpful diagnostic clue. Some episodes may be accompanied by olfactory hallucinations, automatisms, or a brief loss of responsiveness. The duration of the amnestic attacks is usually less than 1 hour but can be longer. In common with other forms of late-onset epilepsy, [25] TEA is responsive to relatively low doses of anticonvulsant medication. However, many patients report persistent memory difficulties after the cessation of attacks. In contrast with TEA, the more widely known syndrome of TGA is characterized by an episode of dense anterograde amnesia, often triggered by emotional or physical stress, which usually lasts 4 to 10 hours and rarely recurs. It is not associated with other focal neurological signs or persistent, clinically significant, memory impairment. [1]

The diagnosis of epilepsy as the cause of recurrent amnestic episodes is often not considered by clinicians. The evidence is most persuasive in those patients with support from all three criteria used in this study: (1) epileptiform changes on the EEG; (2) other features of epilepsy such as olfactory hallucinations, automatisms, or a brief period of unresponsiveness; and (3) a clear-cut response to anticonvulsant medication. In our study, 10 patients satisfied all 3 criteria, a further 38 satisfied 2 criteria, and 8 cases met only 1 criterion. We included this last group, in whom the diagnosis was least certain, on the basis that the clinical features were otherwise identical to those in the other two groups and were thus likely to reflect a common underlying mechanism. Treatment responsiveness is difficult to assess when attacks are infrequent. Five patients experienced fewer than four amnestic attacks, yet met the diagnostic criteria as follows: Cases 12, 22, and 63 had frequent olfactory hallucinations, which disappeared with anticonvulsant medication. Case 73 had frequent spikes over the left temporal region on routine EEG. All had brief episodes of amnesia on waking associated with reports of interictal accelerated forgetting and autobiographical amnesia. Case 116 had three prolonged amnestic episodes, with clear right frontotemporal spikes on sleep EEG together with typical interictal memory complaints. Cases with typical clinical features, but for whom clear evidence of epilepsy was missing, were excluded (see Supplementary Material Case B1 for an example). Other possible causes of tran-

Table 3. Demographic and Neuropsychological Profile of Transient Epileptic Amnesia Patients and Control Subjects

Neuropsychological measure	AF Subgroup (n = 24) Mean (SD)	All Patients (n = 50) Mean (SD)	Control Subjects (n = 24) Mean (SD)
Age, yr	67.0 (8.7)	68.3 (8.6)	67.7 (8.1)
Education, yr	13.0 (3.0)	12.2 (2.9)	12.5 (3.1)
Full-scale IQ, yr	124.3 (10.4)	118.3 (12.8)	120.0 (14.4)
Episodic memory scores (maximum possible score)			
Story recall immediate (25)	16.1 (3.3)	14.0 (4.3)	15.9 (3.8)
Story recall delayed (25)	14.5 (3.0)	11.7 (5.0)[a]	14.7 (3.8)
Story recognition (15)	13.0 (1.2)	12.9 (1.4)[a]	13.6 (1.2)
Rey figure delayed recall (36)	16.3 (5.8)	15.0 (6.5)[a]	18.6 (6.1)
Word recognition (50)	47.8 (2.0)	46.1 (4.7)[a]	48.3 (1.9)
Face recognition (50)	43.3 (3.9)	40.7 (5.4)[b]	45.1 (2.9)
Semantic memory scores (maximum possible score)			
Graded faces (60)[c]	41.3 (8.9)	40.0 (9.6)	44.0 (7.6)
Graded naming (30)	23.2 (3.0)	21.4 (5.1)	23.5 (4.2)
Visuospatial perception score (maximum possible score)			
Rey figure copy (36)	35.4 (1.3)	34.5 (3.1)	35.5 (1.1)
Executive function scores			
Letter fluency (words/3 minutes)	47.9 (11.4)	42.5 (13.9)	43.8 (11.4)
Category fluency (words/min)	21.9 (5.4)	19.3 (5.9)	22.0 (4.4)
WCST categories completed	3.3 (1.3)	2.8 (1.3)	3.4 (1.4)
WCST total errors (percentile)	64.1 (35.1)	52.8 (34.2)	63.4 (32.1)
HAD scores (maximum possible score)			
Anxiety score (21)	6.0 (4.9)	5.4 (3.5)	4.7 (2.8)
Depression score (21)	4.3 (3.3)	4.6 (3.7)[a]	2.9 (1.7)

[a]Significantly different ($p < 0.05$) from control mean; [b]significantly different ($p < 0.001$) from control mean.
[c]For each face: one point for providing identifying information and another for naming. AF subgroup = subgroup of transient epileptic amnesia (TEA) patients selected for accelerated forgetting tests and matched pairwise with control subjects; SD = standard deviation; IQ = intelligence quotient; WCST = Wisconsin Card Sorting Test–64 Card Version; HAD = Hospital Anxiety and Depression scale.

sient amnesia, including transient ischemic attacks, migraine, or psychiatric factors, should always be carefully considered in cases of recurrent transient amnesia, especially when features atypical of TEA are present.

In all the cases described here, transient amnesia was the most prominent feature of the episodes and provided the patients' principal reason for seeking medical assistance. We deliberately included both patients with consistently "pure" attacks of TEA, in which amnesia was the only feature, and patients with episodes in which amnesia was sometimes accompanied by other more familiar manifestations of epilepsy such as brief loss of awareness and olfactory hallucinations. Exclusion of such patients, who were otherwise clinically indistinguishable, would have given a misleading picture of the spectrum of cases with this predominantly amnestic presentation of epilepsy. We did, however, exclude cases where witness accounts were unavailable, unreliable, or indicated more extensive cognitive impairment during all attacks (see Supplementary Material Cases B2 and B3 for examples).

The age at onset of TEA is similar to that of TGA. It is not clear why this age group is particularly at risk for transient memory disorders. The nature of the amnesia in TEA, together with the EEG findings of this and other [8,26] studies, and the high frequency of olfactory hallucinations, point toward dysfunction in the medial temporal lobes for which there is also evidence in TGA. This region is known to play a key role in the acquisition of new memories and the retrieval of re-

A

	Patients (n=24) mean (SD)	Controls (n=24) mean (SD)
learning trials (n)	6.0 (1.4)	5.4 (1.1)
final learning trial recall (%)	97.4 (2.5)	98.5 (2.9)
30 minutes recall (%)	84.0 (10.0)**	92.5 (8.7)
1 week recall (%)	29.0 (28.3)***	66.1 (23.6)
3 week recall (%)	26.0 (27.1)***	63.3 (26.4)

**significantly different from controls (p<0.01)

***significantly different from controls (p<0.001)

B

	Patients (n=20)† mean (SD)	Controls (n=23)† mean (SD)
learning trials (n)	7.9 (2.7)	7.7 (2.7)
final learning trial recall (%)	99.0 (4.5)	94.6 (8.0)
30 minutes recall (%)	91.9 (9.9)	91.5 (6.7)
1 week recall (%)	68.5 (29.5)	74.8 (18.1)
3 week recall (%)	49.0 (29.2)*	65.1 (20.1)

*significantly different from controls (p<0.05)

†4 patients and 1 control did not reach the 90% criterion across 15 learning trials on this task.

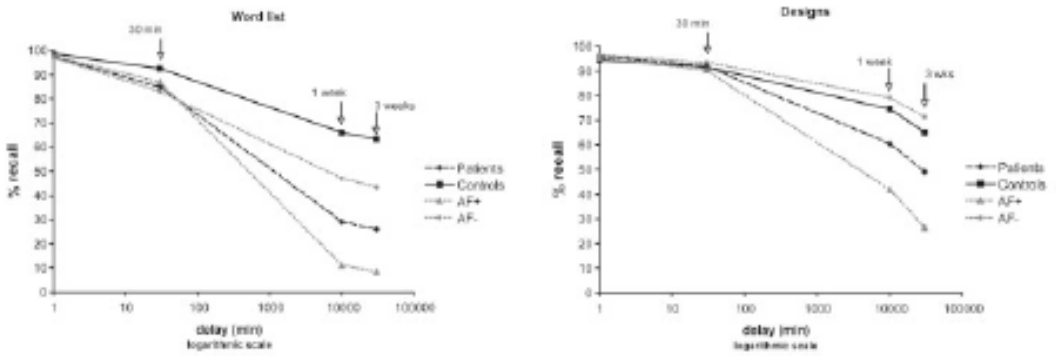

Fig 2. Performance of transient epileptic amnesia (TEA) patients (diamonds) *and normal control subjects* (squares) *on learning and long-term recall of (A) the word list and (B) designs. AF+ = patients with subjective accounts of accelerated forgetting* (triangles); *AF− = patients without subjective accounts of accelerated forgetting* (circles); *SD = standard deviation.*

cent, and possibly remote, episodic events. [27] Cerebrovascular disease is the most commonly identified cause of epilepsy among older patients, [25] and the medial temporal lobes are particularly susceptible to hypoxic damage.[28] Zeman and colleagues [9] note that a history of cardiac disease was common among the patients in their series. In this study, however, we did not find any difference in the presence of overt cardiovascular or cerebrovascular disease between TEA patients and matched healthy control subjects.

Cognitive dysfunction temporally associated with epileptic seizures can be caused either by ictal neuronal hyperactivity or by postictal depression of activity. There is electrographic evidence that both can cause TEA.[8,26,29,30] One patient in our series had an amnesic episode while undergoing EEG. A brief (1 minute) burst of left temporal spikes, during which the patient was unresponsive to speech, was followed by normalization of the EEG and a 10-minute period of amnesia characterized by repetitive questioning about recent events. Although many TEA episodes are longer than usually expected for temporal lobe seizures, persistent electrographic seizure activity has been reported during protracted epileptic amnesia, [26,29,30] and it is recognized that both seizures and postictal dysfunction can be prolonged in older patients. [31]

The mean intelligence quotient in our cohort was in the high average to superior range. This is likely to reflect selection bias: The diagnosis of TEA requires an accurate description of an unusual, transient disturbance of cognitive function. The TEA patient group as a whole was mildly impaired on tests of visual and verbal delayed recall and recognition memory. TEA is, therefore, associated with some decrease in interictal memory performance, but this is subtle. Further work is needed to compare the neuropsychological profile of TEA with other forms of temporal lobe epilepsy. Depression ratings were marginally higher among patients than control subjects, in the absence of any difference in the rates of psychiatric diagnoses. This is unlikely to have influenced the results of cognitive testing.

The subset of TEA patients in whom we studied accelerated forgetting was unimpaired on standard neuropsychological tests or psychiatric measures. Learning rates were normal. However, over delays of 30 minutes to 3 weeks, they showed abnormally rapid forgetting of material learned to a demanding criterion of 90% correct. Furthermore, those patients who had “real-world” complaints of accelerated forgetting showed significantly greater forgetting over the 3-w eek interval than those who did not. Our data thus bear out the patients’ reports of excessively rapid decay of recently acquired memories, and indicate that although this accelerated loss may be detected at 30 minutes, it becomes more apparent over the following days to weeks. This phenomenon, suggesting

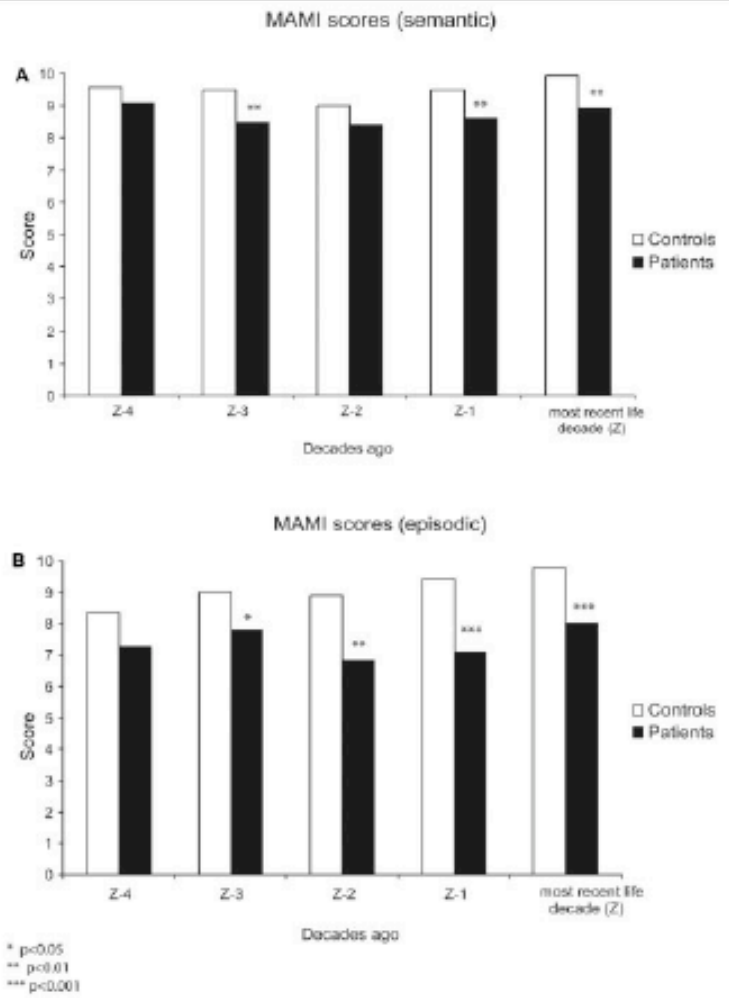

Fig 3. Mean scores of transient epileptic amnesia patients (n = 22; solid bars*) and control subjects (n = 18;* open bars*) on the (A) semantic and (B) episodic memory components of the Modified Autobiographical Memory Interview (MAMI). *p < 0.05; **p < 0.01; ***p < 0.001.*

an impairment of long-term processes of memory consolidation, is relatively novel, but our results are consistent with previous reports of accelerated forgetting among patients with temporal lobe epilepsy.[32–34] The cause is not yet clear. The phenomenon has previously been demonstrated in patients after electroconvulsive therapy, but not in depression without electroconvulsive therapy.[35] Clinical seizures had been abolished in all patients tested and are not, therefore, a necessary condition. High serum levels of antiepileptic drugs have been implicated in the reduced retention of information among patients with refractory epilepsy.[36] However, in this study, patients' memory complaints antedated the initiation of treatment, and anticonvulsant doses were generally low. Our study design did not allow for pretreatment and posttreatment assessment of neuropsychological function, and further work is required to evaluate the relations among accelerated forgetting, clinical and subclinical epileptiform activity, particularly in sleep, and any underlying structural pathology.

We have also demonstrated impaired recall of autobiographical memories acquired many years before the onset of TEA. Once again, this bears out patients' subjective account of their memory difficulties. The occurrence of prominent retrograde amnesia in the presence of normal or near-normal anterograde memory has been termed *focal retrograde amnesia.* Although the explanation is often "psychogenic,"[37,38] focal retrograde amnesia can be caused by a range of

mechanisms in brain disease. [39–41] The autobiographical amnesia seen in the majority of patients with TEA represents a distinctive subtype of "neurogenic" retrograde amnesia. The neural basis of autobiographical memory is currently the subject of a lively debate between proponents of the "standard theory," [42] which proposes that the medial temporal lobes play a temporary role in episodic memory, and "multiple trace theory," [43] which holds that the medial temporal lobes are required permanently for episodic memory recollection. In TEA, the cooccurrence of transient amnestic seizures, accelerated forgetting, topographical amnesia, and autobiographical amnesia in patients with a presumed seizure source in the medial temporal lobes lends some support to the multiple trace theory and provides an opportunity to test the predictions of this hypothesis.

Panayiotopoulos defines a medical syndrome as a "distinct group of symptoms and signs which, when associated together, form a characteristic clinical picture or entity." [44] We propose that TEA represents a distinctive but underrecognized syndrome characteriz ed by recurrent brief amnestic attacks occurring in the second half of life, often associated with accelerated forgetting and autobiographical amnesia. These features provide preliminary grounds for regarding TEA as an "epilepsy syndrome" as defined by the International League Against Epilepsy, [45] pending clarification of the distinction between TEA and other forms of temporal lobe epilepsy occurring in later life. Further work is required to determine the cause of TEA, the underlying mechanisms of accelerated forgetting and autobiographical amnesia, the extent to which these phenomena can account for memory complaints in other forms of epilepsy, and potential avenues of therapy for these types of persistent memory impairment.

Appendix: Three case reports that demonstrate common features of TEA

Case 1 (ID number 28)

A 58 year old carpet fitter experienced 28 episodes of transien t amn esia over 18 months. All occurred upon waking in the night and lasted about 20 minutes. He repetitively questioned his wife, but was responsive and coherent throughout. During one attack he was unable to recall the death of his brother a few days earlier. Routine EEG and MRI were normal. Lamotrigine abolished the attacks but they briefly returned, with associated olfactory hallucinations, during a period of n on-complian ce, and ceased again when he restarted the medication. At interview, he described rapid forgetting of recently acquired memories, patchy loss of salient autobiographical memories from the past 30 years, such as his wife's abdominal surgery and the wedding of his son, and significant new difficulties navigating around his local area.

Case 2 (ID number 10)

A 69 year old retired teacher of French had 23 episodes of transient memory loss over 2 years. All occurred late in the evening, were heralded by a "woozy feeling", and were characterized by loss of memory for events of the past 2 or 3 days and repetitive questioning. She retained the ability to sight-read piano pieces, translate from French to English and perform mental arithmetic. 30 minutes later, when the amnesia resolved, she was able to remember and record in her diary many details of the episode. MRI of the brain was normal but EEG revealed epileptiform abnormalities bilaterally in the temporal lobes. The attacks ceased on Carbamazepine. However, she complained of persistent difficulties recalling certain events from the distant past, including her daughter being badly kicked by a horse 35 years earlier and a holiday to Kenya 4 years earlier.

Case 3 (ID number 112)

A 55 year old mathematics teacher had only the vaguest recollection of his 6 witnessed episodes of amnesia, 3 of which occurred upon waking and 1 while he was driving. On each occasion, he would say to his wife "I've lost it. Where am I? What day is it?" and tried to "piece his memory back together" over about 30 minutes while continuing with other activities. MRI brain scan was normal. EEG revealed epileptiform abnormalities over the left hemisphere and the attacks ceased on Lamotrigine. He described a dense but patchy loss of autobiographical memories from the past 25 years, including his first holiday abroad in 1980, his daughter's wedding in 1999 and his silver wedding anniversary in 2003. He had also developed pronounced difficulties with route-finding, even in familiar environments.

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