Transient global amnesia – not so rare after all

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Summary

Question: Transient global amnesia (TGA) is characterised by the sudden occurrence of amnesia while lacking other neurological symptoms. Complete remission occurs within 24 hours. The pathogenesis remains unknown. The objective of this study was to evaluate the prevalence of TGA in a primary referral hospital in Uster, Switzerland and examine the accuracy of the diagnostic procedure and outcome.

Methods: We conducted a retrospective review of patients with TGA admitted to the Uster hospital, Switzerland between 1/2005 and 10/2007. Of 8166 patients, 20 consecutive cases fulfilled the diagnostic criteria and were further analysed. We included presenting symptoms, diagnostic tests performed, treatment and outcome. A questionnaire to investigate the treating doctor's knowledge of TGA was conducted. A follow up was conducted in all patients at 19.1 ± 7.1 months after presentation.

Results: The incidence was 6.8/100 000/year. In all patients the symptoms resolved within 24 hours and all patients were seen by a consultant neurologist. Drug related causes were excluded. 25% episodes started after some form of exercise, 20% after emotional distress. All patients underwent cerebral imaging. 76% of the questionnaires sent to in-hospital physicians were returned. Diagnostic criteria of TGA were fully known in 75%. In 30% the diagnosis on admission was not TGA and had to be adjusted during the hospital stay. Follow up showed relapse in 10%.

Conclusion: TGA is a syndrome of which emergency physicians should be aware. The diagnosis is made clinically and the prognosis is good, although relapses may occur. Missed diagnoses may lead to uncertainty in patients and their relatives.

Key words: prevalence; transient global amnesia; general hospital; emergency department

Introduction

Transient Global Amnesia (TGA) is a clinical syndrome first described in 1956 by Bender et al. [1] and is characterised by sudden inability to acquire new information. This results in amnesia. Patients stay alert, attentive and cognition is not affected. Symptoms resolve within the first hours, by definition in less than 24 hours. The incidence is 5 per 100 000 per year [2–4]. It usually affects patients between the ages of 40 and 80 years, with an average age of 62 years. It has no male or female preponderance [2, 3].

If the clinical presentation is typical no further evaluation is mandatory [5]. In unclear cases differential diagnoses have to be excluded as summarised in table 1. In these cases cerebral imaging is required. Currently there is no agreement on the aetiology of TGA, although several theories have been suggested. A wide range of pathologies have been described: focal ischaemic lesions [6], brain tumours [7], vasospasm after migraine treatment [8]. Other authors suggest non-convulsive epileptic seizures, paradoxical embolic events through patent foramen ovale or emotional stress [9–11, 21]. Newer studies suggest venous insufficiency with hypoperfusion of the hippocampus [12–15]. This assumption has been supported since valsalva manoeuvres increase venous reflux

Table 1

Differential diagnosis of TGA.

Infection of the brain (fever, elevated CRP, Leukocytosis)
Prolonged complex partial seizures or non convulsive status epilepticus (amnesia, speech arrest, not fully alert)
Transient epileptic amnesia (TEA) (short episode of amnesia, no longer than 60 minutes)
Head injury / cerebral contusion (contusion marks, retrograde amnesia)
Psychogenic amnesia (young patients, mostly isolated retrograde amnesia)
Stroke in hippocampus and thalamus (somnolence, focal neurological losses)
Intoxication and drug intake (Amnesia, somnolence, toxicological screening)

and therefore intracranial venous pressure in patients with incomplete valves in jugular veins [16, 17]. However, there are no consistent neuroimaging findings in TGA [18–20]. The memory loss is a very dramatic experience for patients and their relatives. It is important that clinicians know the disease and its prognosis to guide them through time until the symptoms disappear. Missed diagnosis or wrong information may lead to unnecessary fear or loss of confidence.

The study aim is to investigate the incidence of the disease and its relapse in our region, assess the diagnostic procedures used and the knowledge of treating physicians.

Materials and methods

Study design

We conducted a retrospective, dynamic cohort-study at the Clinic of Internal Medicine at Uster Hospital, Switzerland. This is a teaching facility and the only hospital caring for 160 000 inhabitants. All patients admitted between January 2005 and October 2007 were screened for TGA using the International Classification of Disease code (ICD-10: Code G45.4). Patients were identified and analysed according to presenting symptoms, diagnostic procedures, treatment and outcome. TGA was defined according to the criteria by Caplan [10] and Hodges [11] (table 2). All patients were seen by a consultant for neurology.

To evaluate the physician's knowledge of TGA in our hospital all treating physicans working at the clinic for internal medicine of Uster Hospital were asked to answer a short questionnaire about incidence, diagnostic criteria, treatment and prognosis of the disease (table 3). Furthermore diagnosis proposed at hospital admission was compared to diagnosis at discharge.

Definition of vascular risk factors

Vascular risk factors studied were arterial hypertension (treated, or a systolic blood pressure twice measured at ≥160 mm Hg and/or a diastolic blood pressure >90 mm Hg, diabetes mellitus (treated diabetes, or a fasting blood glucose >7.0 mmol/L) on two occasions, smoking >10 cigarettes daily, hypercholesterolaemia (fasting serum cholesterol >6.5 mmol/L). Patients with a history of ischaemic heart disease (angina pectoris or proven myocardial infarction), peripheral vascular disease or cerebrovascular disease (past major or minor stroke) were classified as suffering from arteriosclerotic disease.

Follow-up

A follow up by phone call was conducted in all patients at 19.1 ± 7.1 months after initial presentation. Patients were asked regarding recurrence of amnesia and any vascular or neurological events. There was no loss to follow-up.

Statistics

Data were analysed using means and confidential intervals. The incidence was calculated as events/100 000 inhabitants/year according to the duration of the evaluation period (19 months) and the number of people (160 000) living in proximity of the hospital.

Table 2

Diagnostic criteria according to Caplan and Hodges.

Attack must be witnessed
Acute onset of anterograde amnesia
No alteration in consciousness
No cognitive impairment other than amnesia
No loss of personal identity
No focal neurology or epileptic features
No recent history of head trauma or seizures
Attack must resolve within 24 h
Other causes of amnesia must be excluded

Table 3

Questionnaire about diagnosis, treatment and prognosis of TGA.

Clinical presentation / Incidence	Choice/Returned answer (%)
Incidence <2/100 000/year	5/16 (31%)
Senso-motory losses or dizziness	0/16 (0%)
Isolated Amnesia	14/16 (88%)
Confusion	4/16 (25%)
Typical duration Symptoms 2–3 days	0/16 (0%)
Diagnostic procedure	
Always cerebral computed tomography	7/16 (44%)
Cerebral computed tomography only when cardiovascular risk factors are present	4/16 (25%)
Treatment / Surveillance	
Give Aspirin 100 mg	2/16 (10%)
GCS for 24 hours	5/16 (31%)
Prognosis	
Relapse common	9/16 (56%)
There is known prophylaxis	2/16 (13%)
TGA is associated with stroke risk	3/16 (19%)

Results

Out of 8166 patients admitted to the Clinic of Internal Medicine of the Uster Hospital 23 consecutive cases of TGA were found according to the ICD-10 diagnosis code. One patient was hospitalised twice during observation period; the second admission was seen as a relapse and accordingly included in the follow up. Therefore 22 patients remained in this study for analysis. Review of patients records revealed one patient with new ischaemic lesions in the MRI conducted during the hospital stay, consequently this patient did not fulfil the diagnostic criteria defined by Caplan [10] and Hodges [11] (table 2). Another patient was excluded because epileptic seizures were observed and con-

Table 4

Patients' characteristics and risk factors.

Patient	Age	Sex	Hosp. days	Arteriosclerotic disease	Hypertension	Cholesterol	Diabetes	Smoking	Migraine	Seizure	Sedativa use
1	76	f	1.6	Yes	Yes	Yes	No	No	No	No	No
2	63	f	1.0	No	No	No	No	No	No	No	No
3	66	f	5.0	Yes	Yes	No	No	Yes	No	No	No
4	66	f	3.3	No	Yes	No	No	No	No	No	No
5	58	m	1.0	No	No	No	No	No	No	No	No
6	86	f	3.8	No	Yes	No	No	No	No	No	No
7	74	f	5.1	No	Yes	No	No	No	Yes	No	No
8	61	f	1.5	No	No	No	No	No	Yes	No	No
9	64	f	1.6	No	No	Yes	No	No	No	No	No
10	58	f	1.6	No	Yes	Yes	No	Yes	No	No	No
11	68	m	2.0	No	Yes	Yes	No	No	No	No	No
12	75	m	2.0	No	No	No	No	Yes	No	No	No
13	62	m	2.8	Yes	Yes	No	No	No	No	No	No
14	71	f	1.1	No	No	No	No	No	No	No	No
15	63	f	1.9	No	Yes	No	No	No	No	No	No
16	61	m	1.8	Yes	Yes	No	No	No	No	No	No
17	75	f	4.2	No	Yes	No	No	No	No	No	No
18	69	m	4.0	No	No	No	No	No	No	No	No
19	64	m	4.2	No	Yes	No	No	No	No	No	No
20	59	m	1.3	No	No	No	No	No	No	No	No
Total/ Mean	67 ± 7.3		2.5 ± 1.4	4 (20%)	12 (60%)	4 (20%)	0 (0%)	3 (15%)	2 (10%)	0 (0%)	0 (0%)

firmed by a pathological EEG in an ambulatory setting three days after hospitalisation. Therefore 20 patients remained for the analysis, what leads to an incidence of 6.8/100 000/year. The mean age was 67 ± 7.3 years, 60% were women. Duration of hospital stay was 2.5 ± 1.4 days.

25% of episodes started after physical activity, 20% short after emotional distress. In all other cases (55%) no specific circumstances could be determined. Other causes for amnesia such as medication, such as benzodiazepine or drugs were absent in all patients.

As shown in table 4 vascular risk factors were notified in 70% (hypertension 60%, smoking 15%, hypercholesterolaemia 20%), none of the patients were diabetic. A history of vascular events was found in 20% of patients (stroke 15%, myocardial infarction 5%, peripheral vascular disease 0%). Migraine history was present in two patients. Ischaemic or haemorrhagic lesions were searched by cerebral computer tomography in all patients. 85% of the examinations were normal, 15% showed old but no new ischaemic lesions. Diffusion-weighted Magnetic Resonance Imaging performed in two cases was normal. Depending on clinical probability vascular duplex ultrasound of the extracranial arteries was performed in 50% of patients. One examination showed a significant stenosis (80%). This patient was sent for evaluation for carotid stenting after hospitalisation.

In medical records none of the patients had ECG proven atrial fibrillation or other significant arrhythmia. ECG on admission showed sinus rhythm in all cases. 24 hour ECG Holter examination was performed in 40%. No relevant arrhythmia was found.

Diagnosis made at hospital admittance was TGA in 14 cases (70%). The other 7 Patients (30%) were hospitalised with other diagnoses (one (5%) with suspected epileptic seizures, 3 (15%) with minor stroke and two (10%) with unspecific confusional state). The reevaluation through a senior physician and the neurological consultant led to establishing the correct diagnosis.

The results of the questionnaires sent by email to investigate physicians' knowledge of incidence, diagnosis, treatment and prognosis are shown in table 3. Return quote was 76% (16 of 21). 75% of the physicians gave fully correct answers regarding the definition criterion for TGA. Almost half would perform a cerebral computer tomography in any case. Relapses are underestimated by 44%. Furthermore 13% believe that there is a connection between TGA and ischaemic disease, for that reason two physicians would start treatment with aspirin.

Follow-up by phone was done 19.1 ± 7.1 months in all of the 22 patients after initial diagnosis and showed relapse of TGA in 10% (2 patients). Calculated one year relapse rate is 6.3%. Apart from the one patient mentioned above, who was newly diagnosed for epilepsy, no neurological or vascular events occurred during this period.

Discussion

20 patients found by their diagnostic code fulfilled the diagnostic criteria. This equates to an incidence of 6.8/100 000/year, what corresponds well to data in literature [4, 20].

The symptoms present in a dramatic manner with abrupt onset of memory loss of recent events and inability to retain new information, which resolves spontaneously within 24 hours. Anterograde amnesia is the main neurological deficit, but some patients may also experience retrograde amnesia which will recover first and rarely exceeds some hours. The diagnosis of "classical" TGA can be clinically immediately suspected when an otherwise obviously healthy patient without other neurological signs is relentlessly asking "what are we doing here, why am I here, what did you say, etc.", accompanied by moderate agitation. Another clinical test supporting the diagnosis of TGA consists of giving a list of 5 to 8 words to memorise to the patient after he seems to have recovered, and had become calmer and stopped asking repetitively. He will be unable or have substantial difficulties to recall these words after 5 to 15 minutes for about 24 hours after the start of the TGA episode. The memory loss is dramatic to patients and their relatives. Proper information about the diagnosis and the prognosis prevents unnecessary fear. Therefore it is important that TGA is known to emergency physicians. According to our questionnaire 75% of residents in our hospital know the main diagnostic criteria. That reflects that only 70% of the diagnoses at hospital admittance were made correctly. Short in-hospital surveillance is often necessary because

amnesia may persist for 24 hours. Since isolated amnesia has no differential diagnosis besides intoxication by medications, patients may be released from hospital as soon as the amnesia resolves. If there is uncertainty about the diagnosis, it is important to exclude differential diagnoses (table 1). According to neurological guidelines[5] cerebral imaging is not mandatory if the diagnosis is clear, but being a clinically defined syndrome TGA may be associated with cerebral lesions and they could be indistinguishable on the basis of clinical presentation. All of our patients received a cerebral computer tomography on admission to hospital. There are data suggesting hypoperfusion of the hippocamal region as cause of the disease [12–15]. Since changes in these tiny structures may not be detected in CT scans. Thus, cerebral imaging – if done at all – should be magnetic resonance imaging. A recently published MRI Study by Sedlaczek [22] suggests these lesions are generally not visible until 48 hours after the event has begun. MRI in our patients was performed within the first 24 hours, therefore we found no lesion.

Different pathophysiological mechanisms are considered none of which sufficiently explain the enigmatic features of TGA [23].

A recent review study by Quinette et al. [24] suggests there are three different groups of patients with different pathophysiological mechanism. First a neurotoxic effect, occurring after emotional or physical stress that affects the hippocampal function as in post-traumatic stress disorder, acute stress and some forms of non-amnesic traumatic brain injury. Secondly some cases occur in context of insufficient jugular-vein valves and precipitating Valsalva manoeuvre [15] and thirdly in patients younger than 56 years might be linked to migraine.

If clinical hints for other causes are missing no further examinations are requested [25]. Arteriosclerosis risk factors were found often (70%) in our patients, 20% had records for a vascular event (stroke, myocardial infarction, peripheral vascular disease). Other studies show similar rates [26]. According to the literature [26–33] TGA itself is not associated with arteriosclerotic risk factors. There is no clear recommendation about further diagnostic evaluations of the risk factors for ischemic disease in patients with TGA [5] but since treatment is different, the distinction to stroke and its risk factors is very important. In our patients 40 to 50% further investigations have been done, especially 24 hour Holter ECG and vascular duplex sonography. Although there will be a substantial proportion of patients with abnormal findings, most are likely to be related to cardiovascular disease but unrelated to the TGA. The findings do not predict recurrence of TGA. In a case of "classical" TGA no paraclinical examination is necessary and should therefore not be performed. Such

Figure 1

Flowchart of inclusion and follow-up.
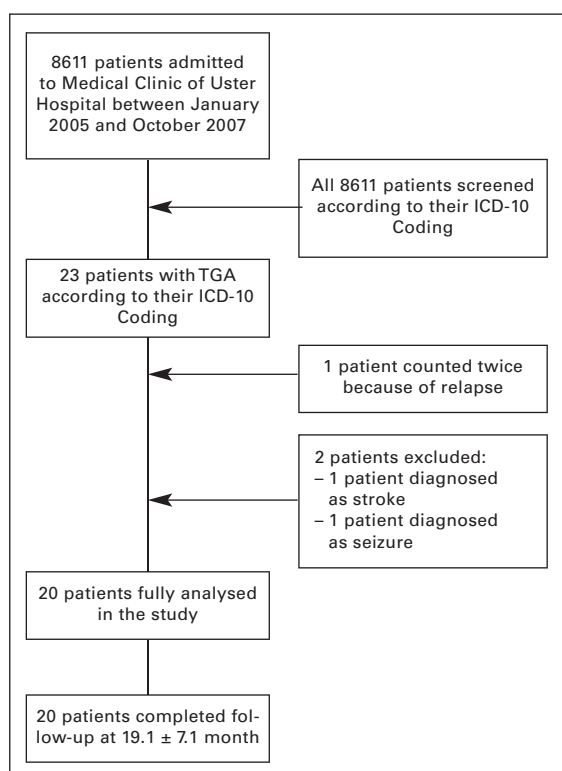
tests raise costs and frighten patients and their relatives during the confessional period.

The prognosis of the disease is good, although relapses may occur. In this study's follow up recurrence of TGA was noted in 10%. This matches well with earlier data [10, 24, 34]. Since there is no treatment it is important that patients and their family are well informed about the illness and its good prognosis.

There are certain limitations in this study: patients were treated by different doctors. Since patients were identified according to the ICD10 Code at hospital discharge, misdiagnosed and miscoded patients were not identified and therefore not enrolled in the study leading to an underestimation of disease incidence. Although the diagnosis was made with the same diagnostic assessment, differential diagnoses were excluded according to clinical probability and the judgment of the treating physician. The small case number reduces the statistical power of the evaluation. Owing to the low incidence a longer surveillance period would be needed to recruit more cases with TGA in our region.

Conclusion

TGA is a common disease which should be recognised by clinicians and emergency physicians. TGA should be included in teaching curricula to minimise unnecessary evaluations and to optimise patient information. The symptoms present in a dramatic manner with abrupt onset of memory loss for recent events and inability to retain new information. Amnesia resolves spontaneously within 24 hours. Current data suggest several risk factors such as migraine, neurotoxic affection of hippocampal function or venous insufficiency with hypoperfusion of the hippocampus. There is no treatment or prophylaxis for the disease. Patients and their relatives are often frightened and anxious because of the sudden loss of memory. A guidance and explanation of the nature of the illness and its good prognosis through the clinician is important.

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