REVIEW ARTICLE

What does transient global amnesia really mean? Review of the literature and thorough study of 142 cases

Peggy Quinette,[1] Bérengère Guillery-Girard,[1] Jacques Dayan,[1] Vincent de la Sayette,[1,2] Sophie Marquis,[3] Fausto Viader,[1,2] Béatrice Desgranges[1] and Francis Eustache[1]

[1]Inserm—EPHE—, Université de Caen Basse-Normandie, GIP Cyceron, CHU de Caen, [2]CHU Côte de Nacre, Service de Neurologie Vastel and [3]CHU Côte de Nacre, Departement d'Accueil et de Traitement des Urgences, Caen, France

Correspondence to: Prof. Francis Eustache, Inserm—EPHE—, Université de Caen Basse-Normandie, Unité E0218, Laboratoire de Neuropsychologie, CHU Côte de Nacre, 14033 Caen Cedex, France
E-mail: neuropsycho@chu-caen.fr

Since the first reports of transient global amnesia (TGA) were published in 1956, several neuropsychological and functional imaging studies have shed light on different aspects of this neurological syndrome. By establishing diagnostic criteria, Hodges and Warlow (1990b) have made it far easier to identify clinical TGA-related features. However, no comprehensive survey has been yet carried out in order to validate their criteria/findings or provide information about previously unknown features. In the present paper, (i) we review the literature published since Hodges and Warlow's study and seek to characterize the demographic and clinical features of TGA more accurately, (ii) we report 142 personal TGA cases, with supplementary information regarding both episodes and patients, such as precipitating events, associated symptoms and personality, and (iii) we suggest the existence of different groups of TGA patients, on the basis of a hierarchical cluster analysis. This revealed that in women, episodes are mainly associated with an emotional precipitating event, a history of anxiety and a pathological personality. In men, they occur more frequently after a physical precipitating event. In younger patients, a history of headaches may constitute an important risk factor. No link was found with vascular risk factors. The relevance of each of the above-mentioned variables is discussed in the light of our classification. An extensive description of cases from both the literature and our patient population allows us to refine the characterization of clinical TGA features.

Introduction

It was in 1956 that Guyotat and Courjon first described transient global amnesia (TGA). In their study, they took a particular interest in describing the epidemiological characteristics of 16 patients (age, context of occurrence, duration, cognitive disorders, medical history and medical examination). In 1964, Fisher and Adams reported attacks suffered by 17 patients and coined the term 'TGA'. According to these authors, TGA usually occurred in middle-aged or elderly people and was characterized by the abrupt onset of anterograde amnesia, accompanied by repetitive questioning. With the exception of the amnesia, there were no neurological deficits. Attacks lasted a matter of minutes or hours and the ability to lay down new memories was gradually recovered, leaving only a dense amnesic gap for the duration of the episode and often the hours leading up to it.

Ever since these early reports, the neurological community has been fascinated by such temporary attacks of pure memory disorder in healthy adults. Consequently, the 1980s witnessed intensive scientific studies in which larger series of patients were reported [485 cases by Caplan (1985); 320 by Stracciari and Rebucci (1986); 277 by Miller *et al.* (1987)]. Interest was centred on the phenomenology of the attacks and their aetiology, as this particular form of amnesia is sometimes difficult to differentiate from psychogenic, epileptic or stroke disorders. At that time, TGA criteria varied widely, and the published series included a number of patients with lasting neurological symptoms or memory loss, such as those observed in epilepsy or after head injury.

In 1990, Hodges and Warlow (1990*a*) suggested that the aetiological uncertainty of TGA mainly resulted from the lack of both clear diagnostic criteria and well-documented epidemiological studies. They attempted to adress this problem by conducting a study of 153 cases, some of them fulfilling strict diagnostic criteria. They showed that while clinical features were not particularly relevant for separating 'pure TGA' patients from other amnesic patients, meeting the criteria was a significant predictor for a good outcome, as they designated a group of patients with a good prognosis and no higher prevalence of vascular risk factors than in other forms of transient amnesia. Amnesic patients who did not fulfil the TGA criteria had a significantly worse outcome. Since this date, many case reports and group studies have been published, but no comprehensive survey has been carried out in order to characterize the clinical features of this syndrome more accurately.

In the present paper, our first aim was to review the relevant literature published since Hodges and Warlow's article (1990*b*) including both single-case and group studies. Furthermore, as we had the opportunity in our laboratory to examine, both during and after an attack, a series of 142 cases of TGA fulfilling Hodges and Warlow's criteria, our second aim was to extensively describe this series of patients. We have divided our analysis of the original data and the reports in the literature into two parts. The first one concerns the patients, that is, gender, age, number of attacks, risk factors and personality features. The second one concerns the clinical characteristics of the attacks, such as precipitating events, associated symptoms, time of onset, duration and neuroimaging findings. Lastly, we propose that cases of TGA should be placed in different categories, according to the clustering of the aforementioned characteristics, and both the relevance of such a classification with regard to the available neuroimaging evidence and its possible clinical usefulness should be discussed.

Subjects and method
Review procedure
We took into account studies published between June 1990 and May 2005 and indexed in MEDLINE. We searched the database using the keywords 'transient global amnesia', but also included papers from journals that were not indexed (such as *Headache,*

Neurocase before 2001 and a chapter of the *Handbook of Memory Disorders*) and papers without the keyword 'TGA' [e.g. Lane (1997), which uses the term 'recurrent coital amnesia'].

We limited our review to case reports or series (i) published in English; (ii) containing data on adult cases fulfilling Hodges and Warlow's criteria defined as follows: the attack must be witnessed; clear-cut anterograde amnesia during the attack must be present; clouding of consciousness and loss of personal identity must be absent and the cognitive impairment must be limited to amnesia; there should be no accompanying focal neurological symptoms; epileptic seizures must be absent; attacks must be resolved within 24 h and patients with recent head injury or known active epilepsy are excluded. Patients with medical abnormalities such as ischaemic lesion, thrombosis and major electroencephalographic irregularities, and cases of transient amnesia triggered by intracarotid amobarbital procedures, marijuana, cerebral angiography, head injury or associated with Herpes simplex viral encephalitis, meningioma, scleroderma, aortic dissection, cyanotic heart disease or drug intoxication were excluded. We took care to count patients included in different papers only once. Patients described in studies performed in our laboratory are presented in the following section (*see* third part of the Appendix). Given these limits, and when information was provided, we collected demographic data concerning the patients (i.e. gender, age, number of attacks, risk factors and personality features) and the clinical characteristics of the attacks (i.e. precipitating events, associated symptoms, time of onset, duration and neuroimaging findings).

In summary, the analysis of the literature was based on a total number of 1353 patients 35 group studies (n = 1259 patients; *see* first part of the Appendix) and 52 case reports (n = 94 patients; *see* second part of the Appendix). However, as details of demographic and clinical characteristics are not supplied in every case, the number of patients reviewed varies from one section to another. For this reason, the number of patients included is noted in each section.

Study of 142 personal cases
Between 1994 and 2004, we collected data on 142 patients (corresponding to 147 TGA episodes). All were admitted to the emergency department of the Caen University Hospital (CHU) and included after they had given informed consent to the study, which was done in line with the Declaration of Helsinski and approved by the local ethical committee.

Thirty-two of these patients failed to meet the first diagnostic criterion, because the onset of the episode had not been witnessed. A witness was, however, present for part of the attack. One patient had suffered head injury with loss of consciousness the previous year. Another patient began his amnesia after a mild closed head injury without loss of consciousness, but was nevertheless included, as his neurological examination was normal and he had suffered three typical TGA attacks several years earlier (*see* Guillery *et al.*, 2000, for details).

All the patients underwent a standard neurological examination on admission, either during or after the acute phase, and were diagnosed as suffering from TGA. EEG and brain CT scans were performed in the majority of cases, either during or after the episode, in order to rule out any possible cerebral lesion. Some of them were also given a Doppler scan of the supra-aortic vessels. Data were collected from the medical files of 129 of our patients. In 13 cases, the files were not accessible and data about the risk factors were missing. Results are reported in Table 1. One hundred and six EEGs were conducted during or after the episode. Eighty-five (80%) were unremarkable.

Table 1 Results of medical examination (percentage of normality) of patients reported in our population

	During TGA		After TGA	
	n	Normal (%)	n	Normal (%)
EEG	52	86.5	54	74
Brain CT	46	91.3	56	92.8
Doppler	1	100	40	97.5

The remaining 26 revealed minor abnormalities but with no epileptic features. One hundred and two brain CT scans were carried out. Eight (7.8%) revealed minor abnormalities, such as leucoaraiosis (two patients), moderate cortical atrophy (three patients), right frontal lacuna (one patient) and small lesions of the caudate nucleus (two patients). Forty out of 41 Doppler scans of the supra-aortic vessels were normal. One revealed a bilateral stenosis of the internal carotid arteries (80% left, 75% right) in a patient with a normal CT scan and who had had no stroke at follow-up 3 years later. However, we had no opportunity to collect additional data using dynamic duplex sonography, single-photon-emission computed tomography (SPECT) or diffusion-weighted imaging (DWI) techniques. A few patients had positron emission tomography (PET), the results of which have already been published (Baron *et al.*, 1994; Eustache *et al.*, 1997; Guillery *et al.*, 2002).

In order to better understand the relationship between possible predisposing factors and TGA, we recruited a 'control' group. This was made of twenty-one subjects who were gender- and age-matched to the study patients (14 females, age mean = 59.7, SD = 8.4, range = 49–75), and who were seen in the emergency department of the CHU for a variety of acute and transient medical conditions: transient ischaemic attack (TIA), attack of asthma, attack of angina, thoracic pain or fainting. After their consent was obtained, they filled in the same risk factor questionnaire as TGA patients (a list of vascular risk factors, past anxiety/depression history, precipitating events and associated symptoms).

Results
Patient demography
Gender distribution
Hodges and Warlow (1990*b*) noted considerable variations in the gender ratio reported in the literature. Thus, while TGA was more common in men in their series, women tended to predominate in other studies (Melo *et al.*, 1992; Lauria *et al.*, 1997). We did not find any significant gender difference (46.4% men 53.6% women) $[\chi^2(1) = 0.48, P = 0.49]$ among the 1333 patients collected from 52 published case studies (n = 91) and 34 published group studies (n = 1171).

In our own study of 142 subjects, however, women were significantly more numerous $[\chi^2(1) = 16.23, P < 0.0001]$. We recorded percentages of 66.9% women and 33.1% men, which differ significantly from the gender distribution of the French population [52.2% women and 47.8% men out of 34 220 296 subjects between 31 and 85 years old; Institut National de la Statistique et des Etudes Economiques (INSEE, 1999)].

The data about the risk factors (*see below*) may help account for this female predominance, in that personality disorders and migraine antecedents may affect women more (for a review, *see* Lipton and Bigal, 2005; Lepine *et al.*, 2005), thereby favouring the occurrence of TGA. Otherwise, the absence of a female predominance in the literature may be explained by a bias of inclusion due to a focus on a specific issue. In effect, some of the authors were interested in TGA occurring at high altitude or triggered by the Valsalva-provoking activity, and these precipitating factors were exclusively observed in men (Litch and Bishop, 2000; Monzani *et al.*, 2000; Savitz and Caplan, 2002; Bucuk *et al.*, 2004; Schiefer and Sparing, 2005).

Age
Our analysis of age distribution was based on 246 patients described in the literature (52 cases and 9 group studies, comprising 91 and 155 patients, respectively, and in which age was provided for individual patients), and is detailed in Fig. 1A. It confirmed that the vast majority of attacks occur between the ages of 50 and 80 (mean = 60.3, SD = 9.6, range = 21–85).

In our series, the age distribution of our 142 patients was very similar (mean = 63.9, SD = 8.3, range = 32–81; Fig. 1B). TGA was very rarely <40 and >80: the only exceptions were two patients aged 32 and 81 years, respectively, and 96% were between 51 and 80. These data support the common belief that TGA mostly occurs after the age of 50, with an average of ∼61–62 years (Caplan, 1990; Hodges and Warlow, 1990*b*).

We compared the age distribution of our patients with that of the French population as a whole (INSEE, 1999), using individuals from the 31–85 age bracket to compose a 100% baseline (*see* Brown, 1998 for the method). When the overall population percentages were subtracted from the percentage of TGA patients, we found that people aged 56–-75 have a higher risk of experiencing TGA (*see* Fig. 2).

Number of attacks
In most patients, TGA occurs only once. Although recurrences have been reported, several authors have shown that, compared with TIAs, the recurrence rate is very low (Hodges and Warlow, 1990*b*; Kapur, 1993; Zorzon *et al.*, 1995; Zeman and Hodges, 2000).

The annual rate of TGA recurrence varied across studies, from 2.9% (Melo *et al.*, 1992; n = 51; follow-up duration = 39 months), 9.4% (Zorzon *et al.*, 1995; n = 64; follow-up duration mean = 45.6 months), 12% (Pai and Yang, 1999; n = 25, follow-up duration = 102 months), 18.6% (Gandolfo *et al.*, 1992; n = 102; follow-up duration = 82.2 months) and 23% (Klotzsch *et al.*, 1996; n = 53; follow-up duration not given) to 26.3% (Fredericks, 1990; n = 57; follow-up duration not given). This variation mainly depended on the length of the follow-up. A recent study on 51 TGA patients with a follow-up of 7 years reported a risk of TGA recurrence of 8% (Pantoni *et al.*, 2005). Studies conducted before the 1990s (e.g. 40% in Markowitsch's review, 1983) all recorded
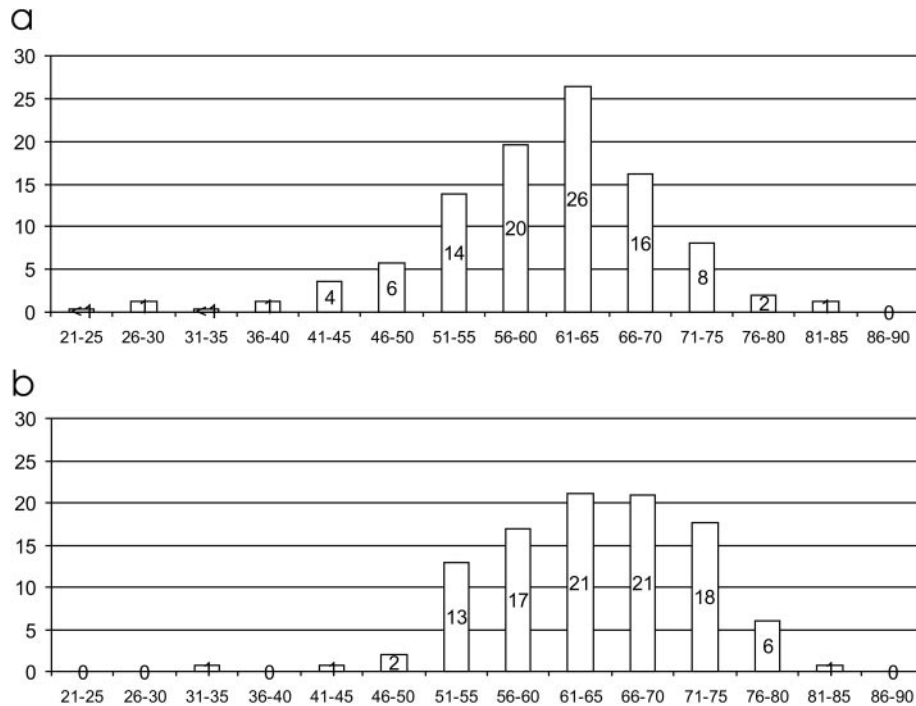
Fig. 1 Distribution (in percentage) of patients reported (**A**) in the literature and (**B**) in our series, according to age.
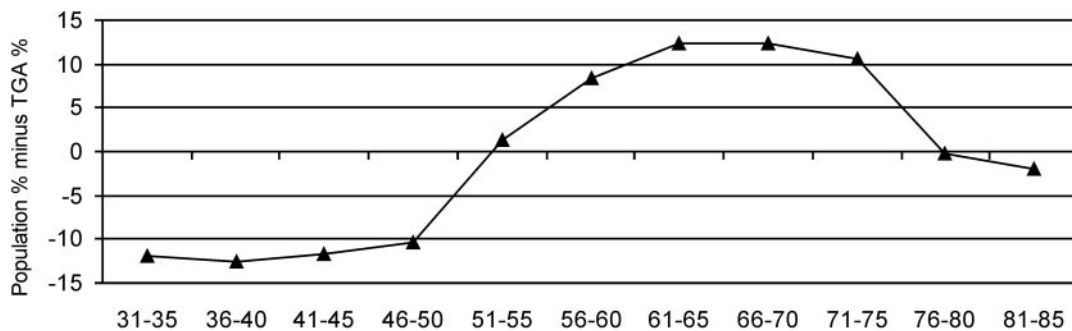

Fig. 2 Difference in age distribution between general and TGA populations.

higher recurrence rates. This discrepancy may result from the inclusion of TIAs in these earlier studies. Data concerning the recurrence are problematic for several reasons: (i) some studies are retrospective; (ii) the duration of follow-up in prospective studies varies considerably, both across patients and across studies, and is sometimes not known.

In 35 group studies (n = 1259) and 52 case reports (n = 94 patients) recurrences were noted for 138 patients (10.19%). Details are only available for eight case reports, and these show that individual recurrence rates were low: six patients had two attacks (75%) and only two had four or six episodes. We thus only made an estimation of the annual rate of our patients taking into account only the medically confirmed recurring TGA attacks weighted by the total number of patients.

In our series, 5 out of 142 (3.5%) patients recruited between 1994 and 2004 had a second episode of TGA. Intervals

between the two attacks varied from 1 month to 1 year. Four other patients said that they had had a previous episode, though without any confirmation from a doctor. If we take these probable episodes into account, the percentage of recurrence was 6.3% (9 out of 142 patients). The calculated annual rate of confirmed recurrence is 5.8%. However, this is only an estimation owing to the absence of any systematic follow-up on our part.

Risk factors

The two main hypotheses put forward so far to explain the enigmatic pathogenesis of TGA are transient ischaemia (for a recent review, *see* Felix *et al.*, 2005) and spreading depression of cortical electrical activity (Olesen and Jorgensen, 1986). One method used to address this issue is to compare TGA patients with matched populations affected by either stroke
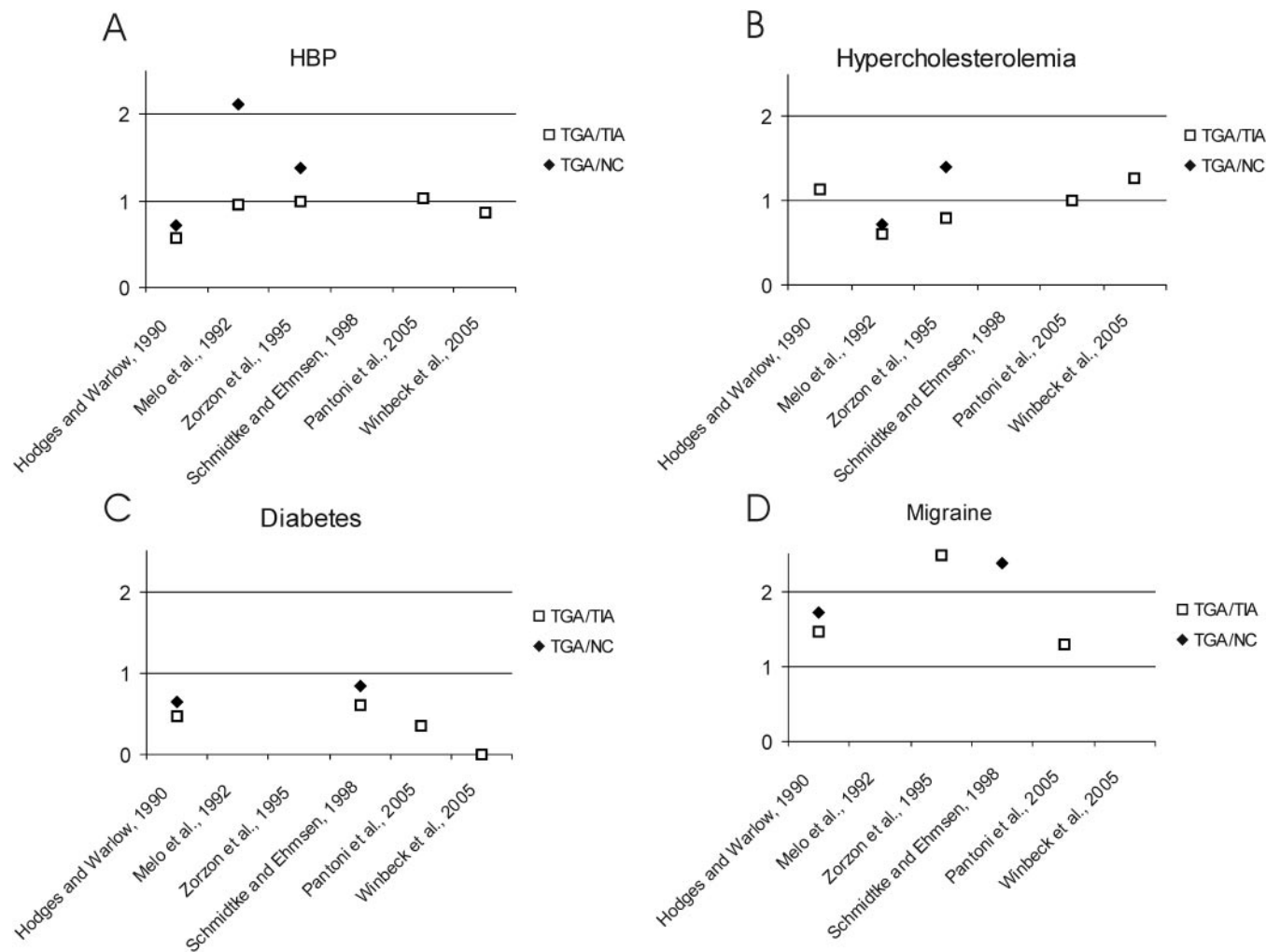
Fig. 3 Results of six group studies that investigated the frequency of risk factors in TGA compared with transient ischaemic patients and/or normal controls. For each study, we calculated the relative risks (i.e. the percentage difference of vascular risk frequency between TGA group on one hand and TIA and normal controls on the other hand) for HBP (**A**), hypercholesterolamia (**B**), diabetes (**C**) and migraine (**D**). While the value 1 means equal risks in both groups (TGA *versus* TIA or NC), a relative risk of 2 means that TGA is more frequently associated with risk factor compared with TIA or normal controls. HBP = high blood pressure; TIA = transient ischaemic attack; NC = normal controls.

or migraine (in which spreading depression is currently the proposed mechanism of aura symptoms).

Six groups have carried out these studies in a series of TGA patients. Only one of them found a significantly higher frequency of isolated high blood pressure (HBP; Melo *et al.*, 1992) in TGA patients compared with normal controls (Fig. 3A). Lauria *et al.* (1998) found that TGA patients suffered more frequently from diabetes than controls. However, no details were given. Regarding hypercholesterolaemia, there was no difference between TGA patients and controls (Hodges and Warlow, 1990*a*; Zorzon *et al.*, 1995). These three factors were useful for distinguishing patients with transient ischaemic accident (TIA) from those with TGA (Hodges and Warlow, 1990*a*; Melo *et al.*, 1992; Winbeck *et al.*, 2005) (Fig. 3B and C). The only factor significantly associated with an increased risk of TGA compared with normal subjects (Melo *et al.*, 1992; Schmidtke and Ehmsen, 1998) and TIA

patients (Hodges and Warlow, 1990*a*; Zorzon *et al.*, 1995) was migraine (Fig. 3D).

We supplemented these studies by taking into account every published case that mentions at least one risk factor. Consequently, analyses were carried out on 19 group studies (including the six above-mentioned studies; n = 779) and 47 case studies (n = 81). Results are shown in Fig. 4A.

In our series, the medical history of 129 out of 142 patients was systematically screened for HBP, hypercholesterolaemia/ hypertriglycaemia, diabetes and headaches/migraines (*see* Fig. 4B). Only 33 patients had no medical history. HBP was reported in 43%, hypercholesterolaemia in 30%, diabetes in 5% and migraine in 24%. Our results are consistent with those in the literature [$\chi^2(3) = 1.79$, $P = 0.61$].

In the control group, 14 subjects (67%) had HBP, 10 (48%) hypercholesterolemia, 4 (19%) diabetes and 6 (28%) headache/migraine. These results indicated that TGA patients
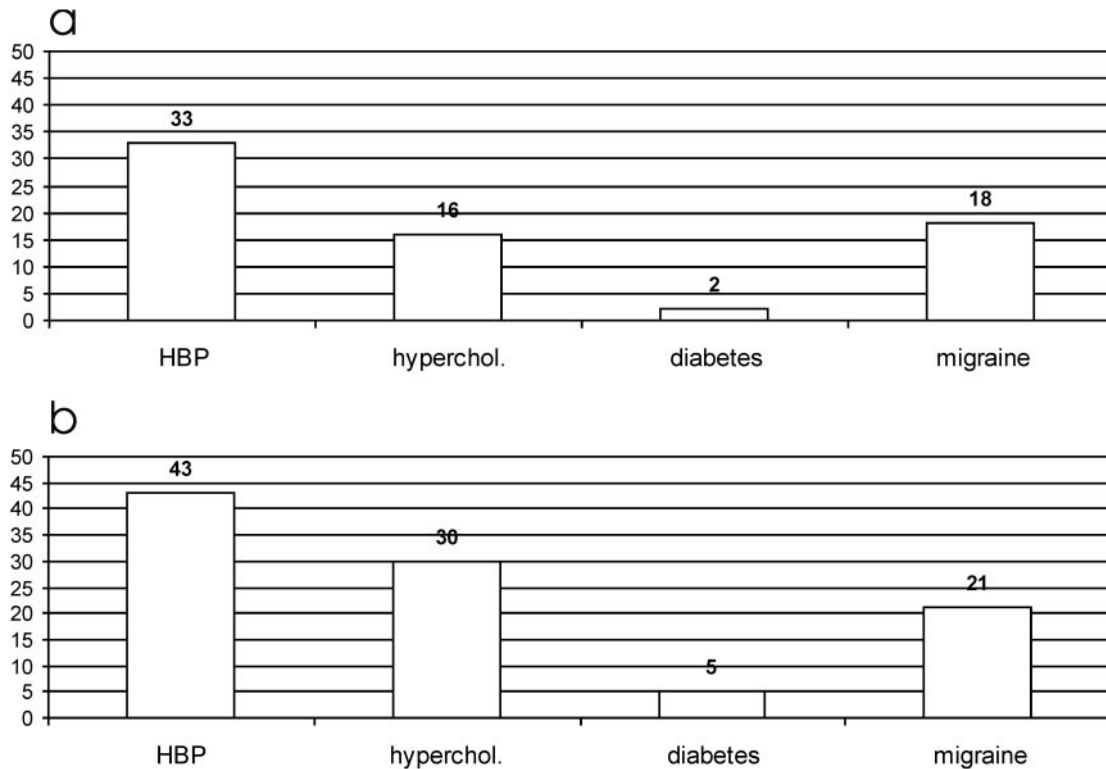
Fig. 4 Distribution (in percentage) of main risk factors for TGA patients (**A**) in the literature and (**B**) in our population. HBP = high blood pressure; hyperchol = hypercholesterolaemia/hypertriglycaemia.

had no more vascular risk factors (i.e. HBP, hypercholesterolemia, diabetes) [$\chi^2(2) = 2.9$, $P < 0.22$] or past migraine history [$\chi^2(1) = 0.17$, $P < 0.67$] than controls.

Personality

Pantoni *et al.* (2005) focused their recent study on the assessment of possible psychogenic aspects of TGA, as already suggested by some authors (Merriam *et al.*, 1992; Inzitari *et al.*, 1997; Kessler *et al.*, 2001). They showed that TGA patients had a higher, statistically significant frequency of psychiatric disease in comparison with TIA controls (39.2 *versus* 13.7%). Only two studies had previously assessed the personality of TGA patients. By means of a geriatric depression scale (Yesavage *et al.*, 1983), Neri *et al.* (1995) showed that 40% (8 out of 20) of their patients had depressive symptoms. The most detailed study was that conducted by Inzitari *et al.* (1997). They investigated the phobic personality traits of 51 TGA patients and established that 82% had pathological avoidance behaviour during phobogenic situations such as the sight of blood, being in crowded department stores or crossing bridges.

In the light of these results, we investigated these psychological features in TGA patients whenever they were reported in the literature. Given the scant attention paid to the personality component, our analysis only concerned 19 group studies (n = 779) and 47 case studies (n = 81). Manifestations of anxiety/depression were recorded in just

2.9% of all these cases, but as it was not systematically researched, we presume that its frequency has been under-reported.

In our population, we also investigated personality, firstly through the medical files. Available for 129 patients, these indicated frequent anxiety/depression past history in 21.2% of the patients. We then used the Mini-Mult [an abbreviated form of Minnesota Multiphasic Personality Inventory developed by Kincannon (1968)] in order to obtain a brief description of our patients' personality. This test was completed by 90 patients but could not be analysed for two patients because of their inconsistent responses and omissions. Interpretation of the remaining 88 tests showed that 41 patients had a normal personality (46.6%), while commentaries were made for the 47 others (53.4%). In accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (American Association of Psychiatry DSM IV, 1994), we defined three categories of personality profiles: (i) Personality disorders as defined by the DSM IV are an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the culture of the individual who exhibits it. Behavioural pattern must cause significant distress or impairment in personal, social, and/or occupational situations (DSM IV). Personality disorders as assessed by the Mini-Mult offer a partial concurrent validity with DSM IV criterion; specifically, some criteria of severity are lacking (Blais *et al.*, 2001). (ii) Anxious/

depressive profile that includes personality with anxious or depressive traits or symptoms; and (iii) emotional instability, a specific category, not related to a specific psychiatric diagnosis, issued from the commentaries of the Mini-Mult, characterized by emotional reactions that are sudden, impulsive and often excessively intense given the trigger stimulus.

Thirty-one out of 88 (35%) patients were found to have at least one of these three specific pathological traits (personality disorders, anxious depressive profile or, more frequently, emotional instability), 16 patients (18.18%) had at least two pathological traits, and all three features were present in 7 of them (7.95%).

In the control group, past anxiety/depression history investigated through a simple questionnaire was found in 10 out of 21 patients (47.6%).

However, the high frequency of psychological and, especially, emotional instability found in our TGA series suggests that some patients might be particularly sensitive to psychological stress. These data reinforce the idea that psychological factors are of particular importance in TGA.

Clinical picture of the attacks
Precipitating events

Fisher and Adams (1964) were the first to take an interest in incidents occurring immediately before the attack, which might help in explaining the cause of TGA. They described several physical precipitating situations, such as swimming in cold water, taking a hot shower, sexual intercourse and pain. In his more recent overview, Caplan (1990) noted the frequent occurrence of emotional stress, pain, angiography, sexual intercourse, physical activity, immersion in cold water, hot baths or showers and driving or riding a motor vehicle. A wide variety of circumstances occurring just before TGA have frequently been mentioned (32% of reports according to Brown's review, 1998), with rarer descriptions of incidents preceding the episode by days, weeks or months (<10% of case reports; Brown, 1998).

Precipitating factors are generally separated into two broad categories, that is, physical and psychological. However, it is sometimes difficult to determine whether an event is physical or psychological. For example, these problems may concern a stressful medical examination (Schmidtke and Ehmsen, 1998), a stressful reaction and pain triggered by aortic dissection (Bonnet *et al.*, 2004) or sexual intercourse (Berlit, 2000). For the purposes of our classification (*see* below), the last factor was grouped with other physical ones.

Out of 881 patients described in the literature (20 group and 38 case studies, n = 827 and n = 54, respectively), precipitating factors were noted in 462 (52.4%) (Fig. 5A).

In our series, a precipitating event was noted in 131 episodes (89.11%). This higher percentage resulted from our systematic search for close precipitating events and the inclusion of other factors, such as anxiety and utter exhaustion, which were not recorded in the literature (Fig. 5C). We regarded

the latter as remote factors because they preceded TGA by several days and contrasted with close factors occurring immediately before the episode (e.g. family worries *versus* sexual intercourse). While remote events were often noted in our study, they seem to have been under-reported in previous studies (Laurent *et al.*, 1990). Often occurring some days or weeks before the episode, they could be regarded as creating a general context of 'psychological pressure'. Figure 5B shows that the distribution of close precipitating factors observed in our population was similar to that reported in the literature.

The category of emotional precipitating factors comprised a variety of events, such as emotional stress triggered by a gastric endoscopy, the announcement of a birth or suicide, a difficult and exhausting work session and even a stressful violin concert. Classic physical precipitants, such as gardening, housework and sawing wood were also found. Contact with water and changes in body temperature occurred during hot baths or shower, a cold swim in the Channel and a session at the swimming pool. A frequently noted remote factor discovered in the weeks before TGA was anxiety resulting from conflict at home or at work, health problems or money worries. Lastly, extremely tiring situations, such as family reunions and the minding of grandchildren, were included in the utter exhaustion category. For some patients, both emotional and physical factors were noted.

Our results match those in the literature, showing that emotional stress, physical effort and water contact/temperature change are the three most frequently observed factors occurring before attacks. As suggested by Caplan (1990), all three share 'some relatively abrupt change' in physical activity, temperature or atmospheric environment, emotional, hormonal or autonomic body response. In addition, we suggest that remote factors may be relevant as well, notably regarding the personality profile of TGA patients.

A comparison with data collected in the control group confirms that TGA occurs in a particular context. We found a significantly different distribution of close precipitating events [$\chi^2(2) = 22$, $P < 0.000$] between TGA and controls. Percentage of emotional stress, physical effort and water contact/temperature change was, respectively, 29, 25 and 14% in TGA series, and only 48, 9 and 0% in the control group. The distribution was also different for the remote precipitating events. Anxiety and utter exhaustion reported in TGA and controls were 24, 6 and 33, 90%, respectively.

Associated symptoms

While clear-cut focal neurological signs are exclusion criteria for TGA, associated symptoms are commonly observed. Hodges and Warlow (1990*b*) suggested that they were mainly limited to headache, nausea and emesis. However, our investigation of the symptoms associated with the episode in 10 group studies (n = 606) and 5 case reports (n = 10) indicated that other symptoms may also be observed. These are set out in Fig. 6A.
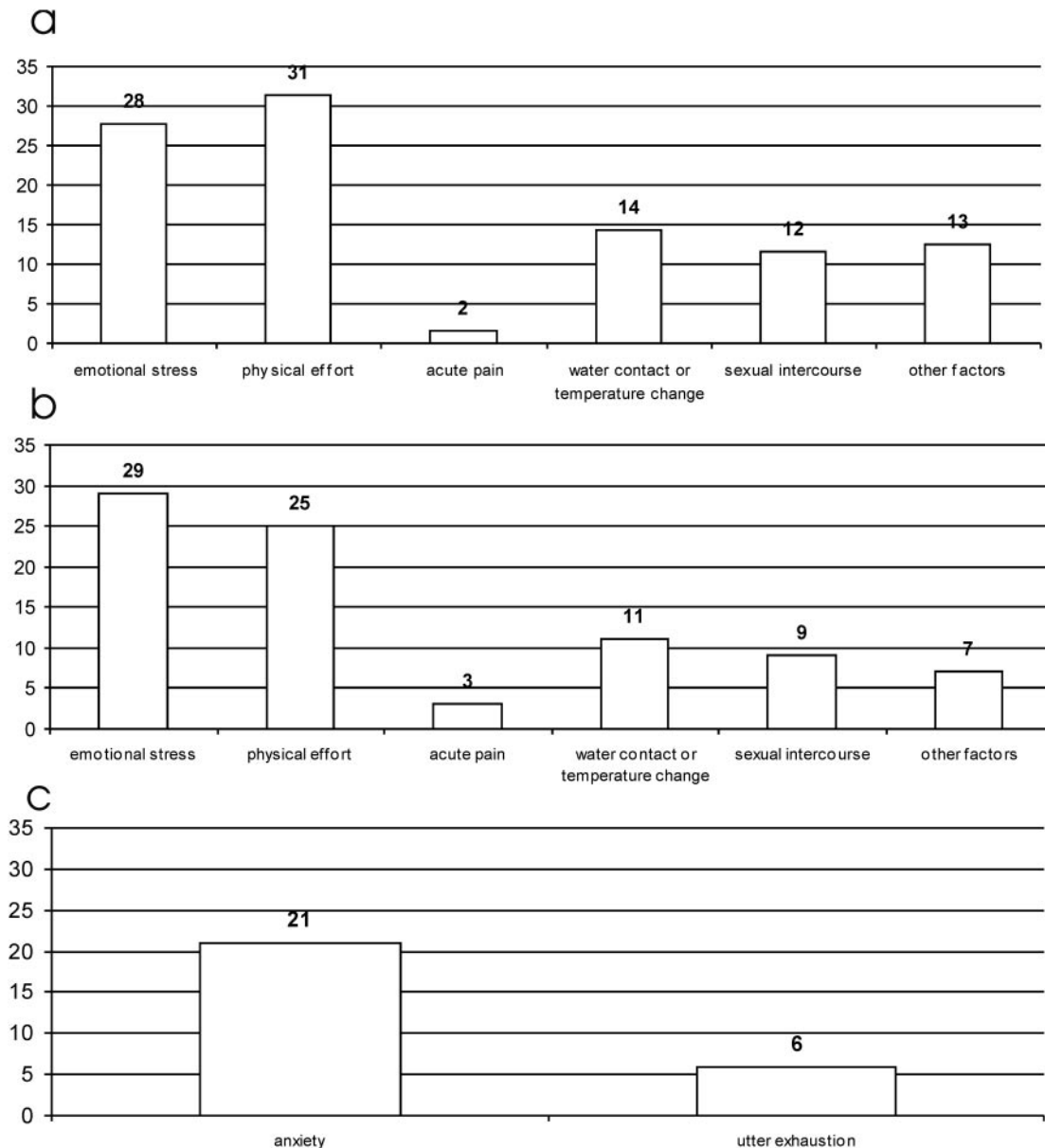
Fig. 5 Distribution (in percentage) of the close precipitating events observed (**A**) in the literature and (**B**) in our population. (**C**) Represents the distribution of the remote precipitating events noted in our patients. Other factors: emesis, defacation, coughing, Valsalva manoeuvre, medical examination, driving or high altitude (in the literature), stopping BZD treatment, overeating, physiotherapy session and emesis (for our population).

Given the absence of any physical origin, plus the presence of several emotional factors (personality disorder, emotional precipitating event and manifest anxiety of patients during the acute phase), we hypothesized that the symptoms associated with TGA might be a somatic manifestation of anxiety. Consequently, to complete the emotional picture of TGA, we decided to perform a systematic investigation of these associated symptoms. Thus, our questionnaire focused on somatic symptoms such as those observed in panic attacks or migraine (Zorzon *et al.*, 1995). Ninety-five out of 122 patients (77.8%) had at least one associated symptom.

Figure 6B shows that, as in the literature, headache was the most typical symptom of TGA, as it was associated with 49 episodes. Other possible somatic symptoms were also reported, such as dizziness (25%), nausea (24%), chills or flushes (16%), fear of dying (14%), paraesthesia or cold extremities (12%) and emotionalism (11%). The presence of these somatic symptoms, which have rarely been measured, highlights the usefulness of investigating the psychological dimension of TGA.

The comparison of the associated symptoms between TGA and controls showed that the frequency of headache was similar [$\chi^2(1) = 1.6$, $P < 0.2$]. However, TGA
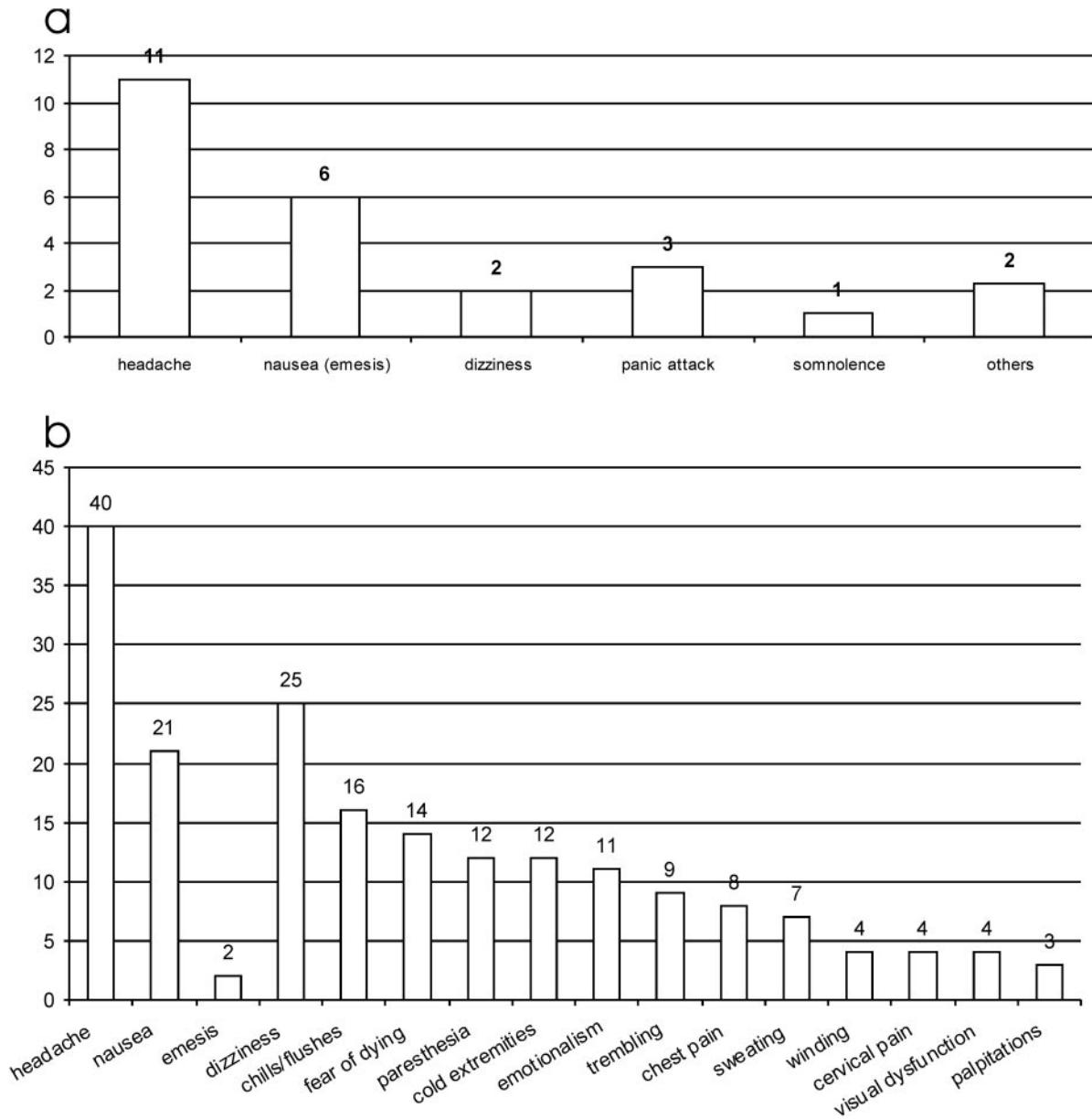
Fig. 6 Distribution (in percentage) of symptoms associated with episodes (**A**) from the literature and (**B**) from our population. Others: trembling, tinnitus, paraesthesia, chest pain, cramp, chills or flushes, and so on.

episodes were more frequently associated with one of the panic attack criteria (DSM IV) (95 versus 5%) [$\chi^2(1) = 79.2$, $P < 000$].

Time of onset
Three group studies suggested that TGA attacks mostly start in the morning (Schmidtke and Ehmsen, 1998; Pai and Yang, 1999; Pantoni et al., 2005). An analysis of 13 other studies (n = 17), in which the exact time of onset was reported, confirmed these observations (Fig. 7A).

In our patients, TGA was more likely to occur in the morning or at midday [$\chi^2(2) = 21.79$, $P < 0.0001$] (see Fig. 7B). Amnesia is obviously not detectable during sleep, but no patient was reported to have woken up in a 'TGA state', or to have started a TGA while awake between midnight and 6 a.m.

We found no information in the literature about the day of the week and our results showed that TGA could occur on any day [$\chi^2(6) = 4.66$, $P = 0.58$].

Lastly, an analysis of 46 patients (from 1 group study and 16 case studies), regarding seasonal distribution revealed a peak of TGA occurrence in spring and summer [$\chi^2(3) = 9.91$, $P = 0.01$] (Schmidtke and Ehmsen, 1998; Tubridy et al., 1999) (Fig. 8A).
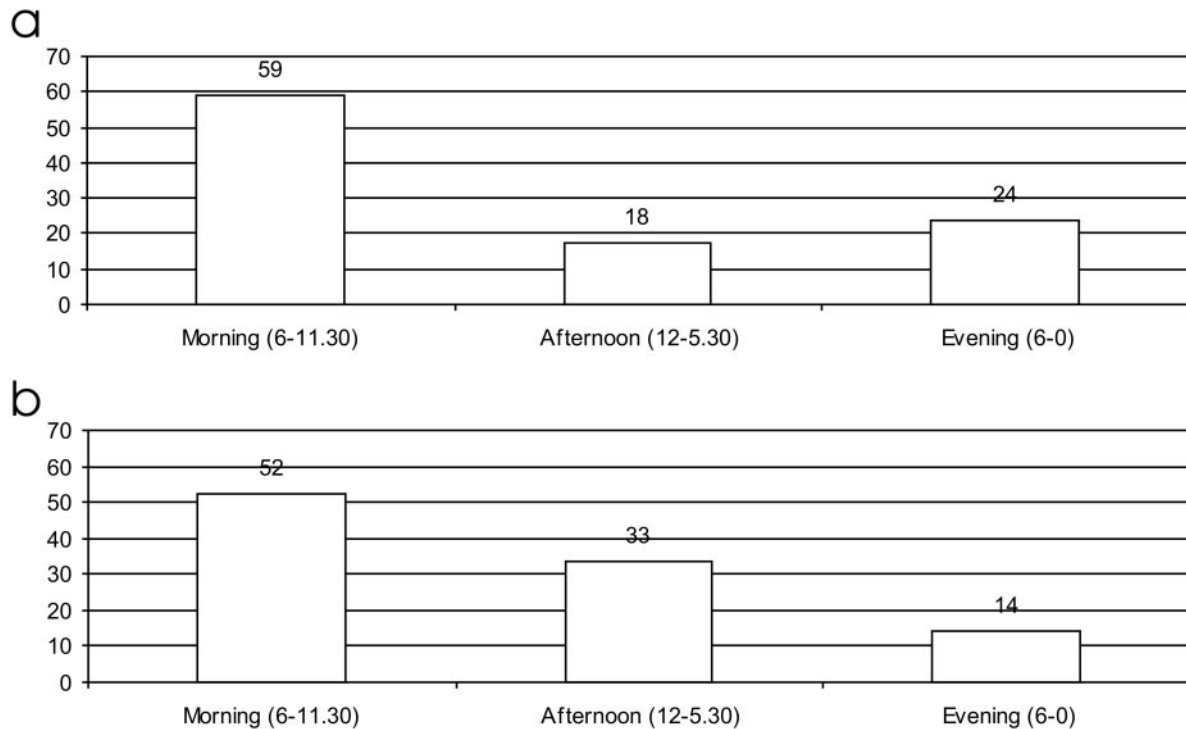
Fig. 7 Distribution (in percentage) of episodes (**A**) from the literature and (**B**) from our population, according to the time of day.

This predominance was not observed in our cohort, whose episodes were evenly distributed throughout the year (Fig. 8B) $[\chi^2(3) = 2.03, P = 0.56]$.

Duration

The exact duration of TGA is often difficult to measure accurately. While the onset of the attack is usually easy to pinpoint when it is witnessed because it is so sudden, recovery is gradual and there is no criterion to determine the time when TGA comes to an end.

Nevertheless, the duration of amnesia is seen as having a diagnostic value in TGA, as Hodges and Warlow (1990b) demonstrated that the brevity of the episode (<1 h) is one of the two most important clinical features predicting epilepsy in the presence of transient amnesia (the other being the multiplicity of attacks).

TGA usually lasts ~4–6 h (Zeman and Hodges, 1997). The mean duration in Hodges and Warlow's series was 4.2 h. Most episodes last between 1 and 8 h. The shortest reported attacks lasted 15 min (Moccia *et al.*, 1996) and the longest 24 h.

Details concerning the duration of 165 episodes (from 37 case studies, n = 65, and 5 group studies, n = 100) showed that 3% lasted <1 h and the majority of episodes lasted between 1 and 10 h (mean = 8.1, SD = 6, range = 15 min to 24 h) (Fig. 9A).

In our study, we measured the duration of amnesia using several types of information. The end of the attack was estimated on the basis of temporal disorientation and the ability to form new memories. When patients were oriented in time and space, and when they were able to explain the reasons for their hospitalization and recall the neuropsychologist's name, we considered that the episode was over. The next day, we checked the duration of the episode by studying the length of the lacunar amnesia.

Out of 145 attacks in which duration was estimated, 3% of attacks lasted <1 h, with the majority of episodes lasting between 1 and 10 h. One episode lasted 16 h. Our mean duration (5.6 h, SD = 3.4, range = 0.5–16 h) was similar to that of Hodges and Warlow's series and our distribution matched that previously reported in literature (Fig. 9B).

Neuroimaging

Three main techniques have been used during TGA: SPECT, PET and DWI.

Studies with SPECT have pointed out haemodynamic changes confirming a transient dysfunction of the medial temporal lobe in 42 out of 43 TGA patients examined during the acute phase (Treig *et al.*, 1988; Fayad *et al.*, 1990; Stillhard *et al.*, 1990; Goldenberg *et al.*, 1991; Tanabe *et al.*, 1991; Evans *et al.*, 1993; Lin *et al.*, 1993; Goldenberg *et al.*, 1995; Kazui *et al.*, 1995; Jung *et al.*, 1996; Sakashita *et al.*, 1997; Schmidtke *et al.*, 1998; Takeuchi *et al.*, 1998; Jovin *et al.*, 2000; Warren *et al.*, 2000; Bucuck *et al.*, 2004; Nardone *et al.*, 2004; Takeuchi *et al.*, 2004). Only three PET studies
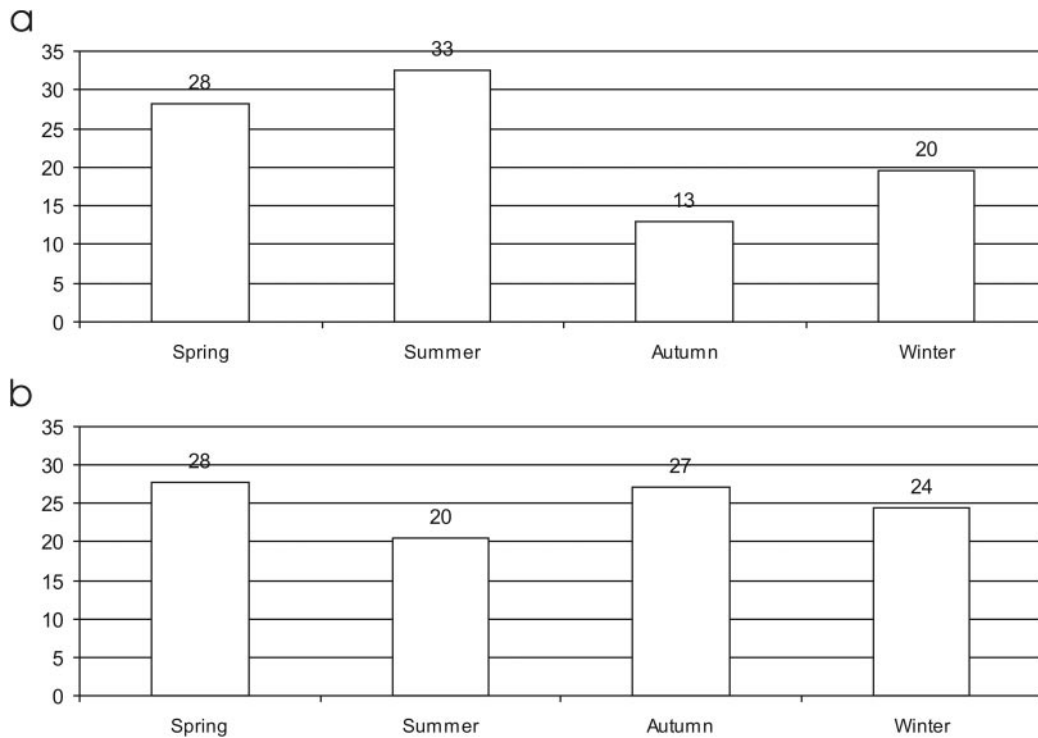
Fig. 8 Seasonal distribution (in percentage) of TGA episodes (**A**) from the literature and (**B**) from our population.
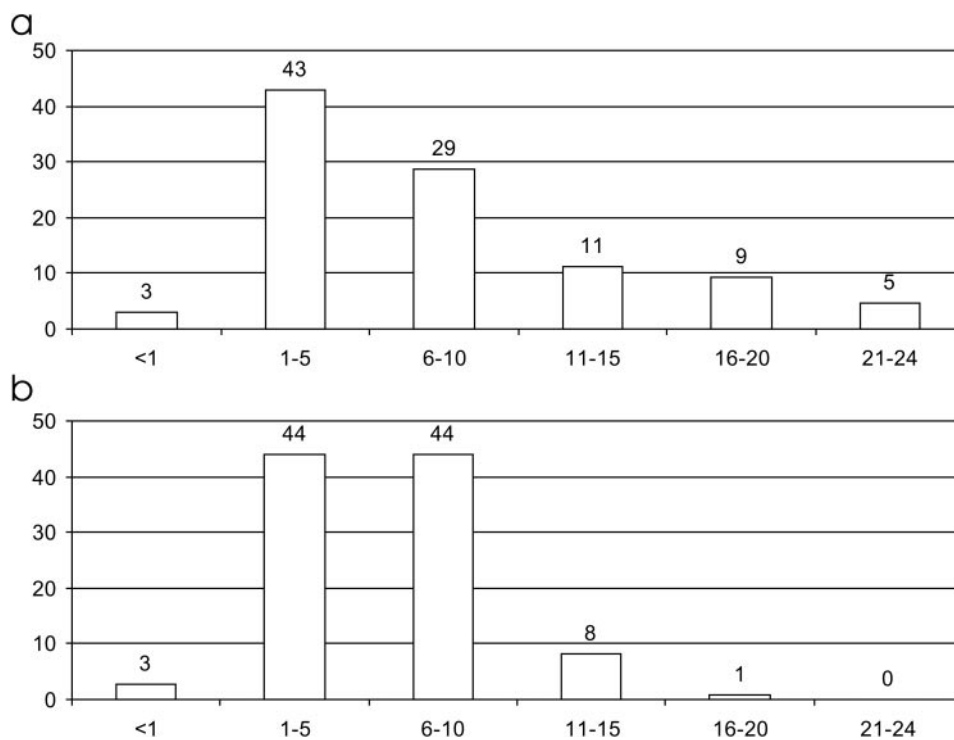

Fig. 9 Distribution (in percentage) of the episodes (**A**) from the literature and (**B**) from our population, according to their duration.

carried out during the acute phase of TGA have been fully reported, and patients came from our population (Baron *et al.*, 1994; Eustache *et al.*, 1997; Guillery *et al.*, 2002). Abnormalities have been found in 4 out of 4 patients

in several regions such as hippocampus, amygdala, lentiform nucleus or neocortex. Involvement of the hippocampus was also demonstrated in a T2 reversed MRI study by Nakada *et al.* (2005). These authors investigated the structural integrity

of hippocampus in 15 patients after an episode of TGA and observed a high incidence of high and giant cavities. Nevertheless, even if these techniques are useful in specifying the site of dysfunction in this disorder, they give no conclusive information about the physiopathological mechanisms *per se*.

The DWI has also been used to investigate the pathophysiology of TGA. This very sensitive technique is commonly used in clinical practice for the early detection of cytotoxic oedema due to ischaemia and seems particularly relevant in TGA. Ninety-three patients were examined using DWI during and/or after an episode of TGA fulfilling the criteria of Hodges and Warlow (1990*b*). However, contradictory findings have been reported and abnormalities were only detected in 55.9% of the patients (Ay *et al.*, 1998; Strupp *et al.*, 1998; Gass *et al.*, 1999; Greer *et al.*, 2001; Huber *et al.*, 2002; Labar *et al.*, 2002; Matsui *et al.*, 2002; Savitz and Caplan, 2002; Saito *et al.*, 2003; Jeong *et al.*, 2003; Ravidran *et al.*, 2004; Sedlaczeck *et al.*, 2004; Winbeck *et al.*, 2005). The most important finding was the consistent location of DWI abnormalities in hippocampal regions (*see* Sander and Sander, 2005 for discussion) but their origin is still a matter of debate. Indeed, DWI is highly sensitive for ischaemia but is not specific. Cytotoxic oedema has been found in other disorders such as hypoglycaemia, cortical spreading depression or epileptic seizure (Fisher and Albers, 1999). Thus, these DWI findings are far from conclusive for the nature of the physiopathological mechanism of TGA.

In summary, these neuroimaging data are conflicting and do not elucidate the aetiology and the physiopathology of TGA. One possible aetiology of this disorder is a haemodynamic vascular mechanism. According to Lewis (1998), TGA could be triggered by venous congestion leading to a cerebral venous thrombosis and a venous ischaemia. Results of a duplex ultrasonography study carried out in a series of 114 cases of TGA support this hypothesis. During a Valsalva manoeuvre, studies have found a high frequency of insufficient jugular-vein valves in TGA patients compared with healthy people, which might favour the occurrence of venous congestion (Sander *et al.*, 2000; Maalikjy Akkawi *et al.*, 2003; Nedelman *et al.*, 2005; Schreiber *et al.*, 2005). Second, a physiopathological mechanism proposed by Olesen and Jorgensen (1986) is spreading cortical depression because of the high prevalence of migraine in some TGA patients (Hodges and Warlow, 1990*a*; Melo *et al.*, 1992) and of the presence of common precipitating factors and headache-accompanying symptoms.

Classification of TGA using multivariate analysis techniques

The discrepancies between neuroimaging studies suggest that there might be some heterogeneity in the pathophysiology of TGA. In an attempt to classify clinical and demographical features associated with TGA, we have carried out a multi-stage analysis procedure on the data collected on our 142 subjects by means of the multiple factorial analysis

(MFA) and the hierarchical cluster analysis (HCA). The MFA and the HCA provide a spatial representation of data that can facilitate interpretations and reveal relationships between subjects or variables. These methods, which were employed to carry out the overall classification, have been used in different fields, including neuropsychology (Mitrushina *et al.*, 1999).

Material and methods

Two parts were distinguished. First, we decided to reduce the number of individual-associated symptoms using a HCA. Second, we made an overall classification with the aforementioned variables using MFA and HCA. The SPSS analysis package (version 14.0) was used for both multivariate analyses.

In the first part, we made a preliminary data reduction by means of a HCA to verify that symptoms associated with the TGA were not sporadically distributed but rather gathered in two entities, namely 'migraine' on one hand and 'symptoms of panic attack' on the other hand. HCA is an exploratory data analysis technique that attempts to determine whether or not a data set contains distinct groups and, if so, to find the groups (Everitt, 1994). HCA aims at sorting different objects (or attributes) into groups in a way that the degree of association between two objects is maximal if they belong to the same group and minimal otherwise. There are different measures of inter-observation distance (also called measure of similarity) and different clustering algorithms (also called measure of linkage between groups or inter-cluster distance). Measures of inter-observation distance available for binary data are numerous. We used Yule's Q, a measure of pairwise association, based on the conditional odds ratio from a log-linear model (Lipsitz and Fitzmaurice, 1994). Yule's Q applied to binary variables is similar to Goodman and Kruskal's gamma. For the measure of similarity (or distance) between two clusters (or groups), we used the most common method, the Unweighted Pair Groups Method Average (UPGMA), that is, the distance between two clusters is the mean of the distance between all possible inter-cluster pairs. Stability of the model was explored by comparing the results of different methods of measuring inter-observation distance (Yule's Q, Jaccard's and squared Euclidian distance) and of different measures of inter-clusters distance (UPGMA, Ward's method).

In the second part, we embarked on the overall classification of the reduced set of associated symptoms and the other remaining variables. As the HCA is an explanatory method, a crucial problem is the choice of the variables entering the final clustering classification. We chose to resolve this difficulty by preceding the HCA by an MFA. This last method allows distinguishing the variables that contribute to the main part of the global variance and their association in a low space dimension. Since MFA makes it possible to represent relations between the variables in graphic form, along dimensions accounting for most of the total variance, our selection included the most diametrically opposed variables. We then performed an HCA on these selected variables.

The MFA, also an exploratory data analysis technique, offers visual and analytical aids for the physician facing complex clinical features. Expert's clinical reasoning may be enhanced by the factorial maps and computerized results provided by MFA. Moreover, the MFA is a way to select pertinent variables to be included in an HCA. We use optimal scaling (Meulman *et al.*, 2004) as the method of MFA. MFA aims to reduce dimensionality with the least possible loss of

information, whereas the interpretation of the extracted dimensions is based on the category of the analysed variables. Because variables are affected by non-linear optimal scaling transformations, the model represents not the original categorical variables but the transformed variables. The missing variables were also replaced by the mode.

Classification of the associated symptoms

Associated symptoms of TGA, almost all of which are also found in migraine and panic attacks, were recorded for 116 out of 142 patients. We only included the first episode in case of recurrence and episodes with complete data. All the symptoms were included as variables in the HCA, except for 'choking', as only one case was observed. Results of the HCA are reported in Fig. 10. The dendrogram shows two major clusters. The first cluster contained the relevant symptoms of migraine: headache, cervical pain, emesis or nausea, cold extremities and sweating. Headache was the most frequent symptom (45 out of 116 subjects). The second major cluster contained somatic symptoms such as those noted in panic attacks. Sixteen out of 116 subjects presented a pure TGA with no associated symptoms of migraine or panic. To assess the stability of the model we used different inter-observation measures (squared Euclidian distance, Jaccard) and obtained the same results: the model was stable. In summary, the statistical clustering of the associated symptoms produced two broad categories, corresponding to migraine and panic attacks, although many symptoms, that is, sweating, nausea, dizziness, paraesthesia and chills, have been observed in both disorders. Only one symptom, concerning four cases—'visual dysfunction'—appeared to have been placed in the wrong category. Six out of 116 subjects (5.2%) met the four criteria needed to establish the diagnosis of a panic attack (DSM IV), and one of them presented a co-occurrence of panic attack and headache.

The results highlighted the involvement of emotional features in numerous TGA patients, as previously mentioned by Inzitari *et al.* (1997), although this is unlikely to fully explain the syndrome's occurrence (Merriam *et al.*, 1992). Our data also showed that only a few patients had a pure amnesia, with most of them presenting additional symptoms. However, the fact that these symptoms did not necessarily include headache suggests that they may result from the episode *per se* rather than as the consequence of a migraine attack.

On the basis of these results, the associated symptoms were restricted to three variables for the MFA analysis, reflecting the symptomatology of migraine and panic attacks: headache, panic attack (including the six patients with the four symptoms of panic attack) and absence of symptoms.

Overall classification of demographic and clinical data

The overall classification of demographic and clinical features was carried out in two steps: first, by means of a MFA, and then by means of an HCA.

For the first step, the following variables were included: gender, age (<56, 56–75, >75 years), precipitating events (emotional, physical and none), three variables representing associated symptoms (headache, panic attack, none), risk factors (history of anxiety, HBP, hypercholesterolaemia, history of migraine, vascular risk factor) and personality (abnormal Mini-Mult, personality disorder, anxiety and emotional instability).

The results are reported in Fig. 11 and show that two dimensions explain 42.81% of the total variance. The fit of the model was appreciated by the Cronbach's alpha coefficient: 0.81. The first dimension (horizontal axis), which regroups the main part of the variance, may be interpreted as a 'psychological dimension' (including the precipitating events, type of personality and gender) and the second one (vertical axis) as a 'somatic dimension' (age,
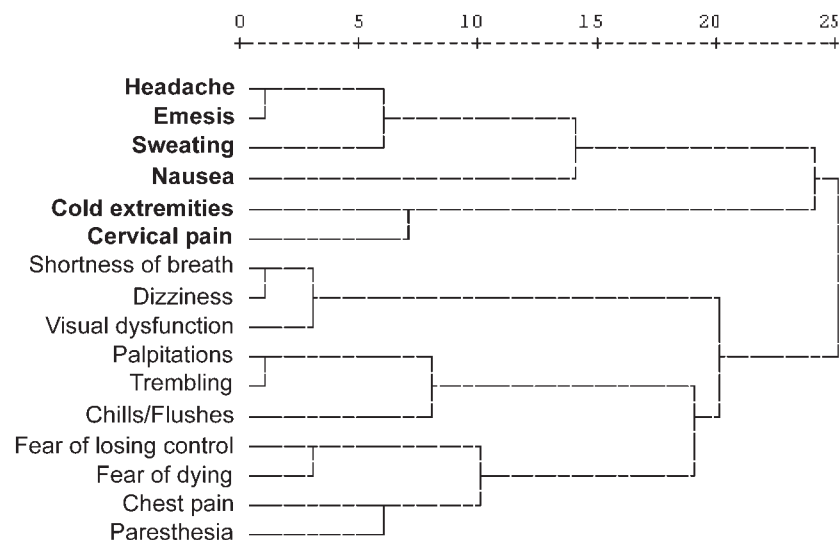

Fig. 10 Dendogram based on the HCA of associated symptoms reported for 116 subjects, using average linkage (between groups). The classification produced by the HCA technique is illustrated by the present dendrogram: it is a tree diagram where the rescaled distance between two clusters is indicated on the horizontal axis. Shorter the distance, closer are the clusters. The horizontal axis denotes the linkage distance. Distance is calculated and rescaled from 0 to 25 according to the measure of similarity (Yule's Q) and the cluster algorithm (average linkage). Distance between two clusters (or variables) is read between two vertical traits. Thus, for each node in the graph we can read off the distance at which the subclusters were linked together in a new cluster. The dendrogram shows two major clusters: (i) symptoms of migraine: headache, cervical pain, emesis or nausea, cold extremities and sweating; (ii) somatic symptoms such as those noted in panic attacks.
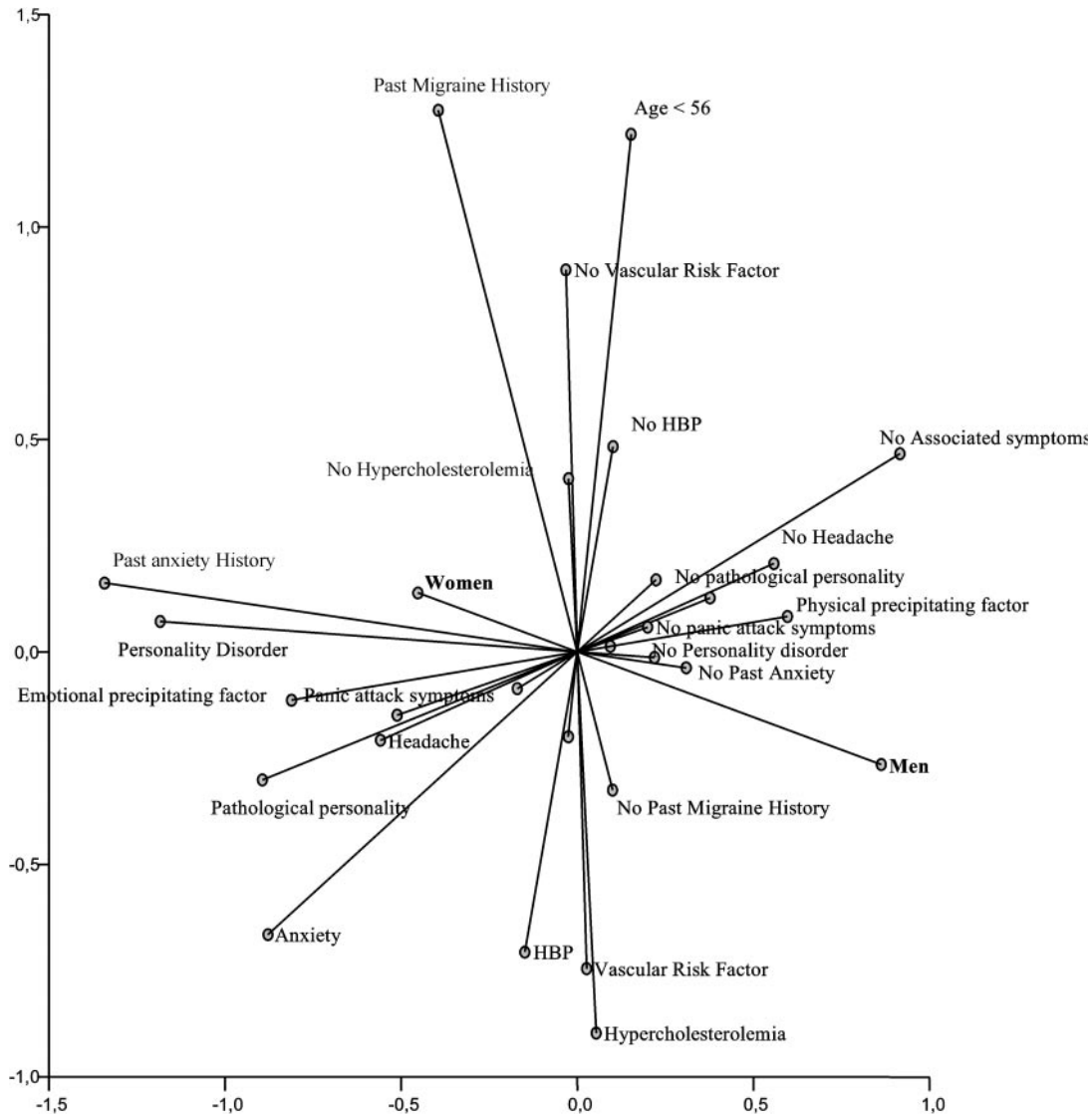
Fig. 11 Graphical representation of the MFA results. The variables are reciprocally represented in a 2D space, and each variable is associated with a set of component loadings, one for each dimension. The independent dimensions and the distance information assign order and spacing among the nominal values and allow interpreting relative positions and orientation of the objects and of the transformed variables. The MFA provides also the 'coefficient loadings' associated with the variables that allow interpreting the variables mostly contributing to the axis. For the first dimension (horizontal axis), the variables with the highest coefficient loadings (higher than 0.5) are 'precipitating factors', 'gender', 'past anxiety history', 'associated symptoms' and 'psychopathology'. For the second dimension (vertical axis), 'vascular risk', 'past headache history' and 'age' are the main variables. Some other grouping of the modalities of the variables could be observed: (i) On the first dimension, men, a physical precipitating event, no risk factor and no additional symptom during the episode of TGA contrasted with women, an emotional precipitating event and psychological risk factors. (ii) On the second dimension, age <56 years and a history of migraine contrasted with vascular risk factors.

vascular risk factors and history of headaches). These results clearly appeared on the diagram (Fig. 11) that shows additional relations between the modalities of the variables: on the first dimension, men with physical precipitating events and no associated symptom contrasted with women and emotional factors. On the second dimension, younger patients with a history of migraine contrasted with vascular risk factors. It is worth noting that headache during the episode of TGA was not linked with a history of migraine, confirming that the two are quite distinct.

The second step consisted of an HCA intended to better characterize the associations suggested by the MFA. Variables were selected according to the results of the MFA and concerned gender, age, precipitating events, medical history, personality and associated symptoms. The dendrogram (Fig. 12) shows four principal clusters. The first associated women with psychological factors and the second groups together patients aged <56 years and ones with a history of migraine. The third cluster brings together men, patients without any risk factors or associated symptoms, and physical precipitating events. Lastly, the fourth cluster comprises the vascular risk factors.

In summary, the results of the overall classification provide a comprehensive overview of the clinical entity TGA.
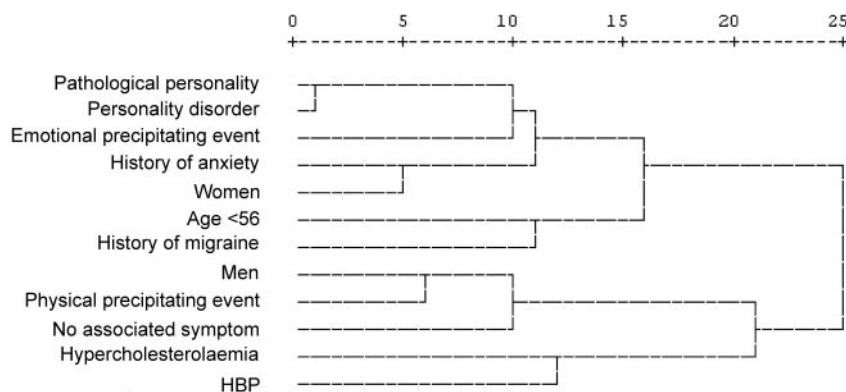
Fig. 12 Dendrogram based on the HCA of demographic and clinical data from 63 patients, using average linkage (between groups). Four principal clusters were observed: (i) women with psychological factors, that is, personality and precipitants; (ii) patients aged <56 years and ones with a history of migraine; (iii) men, patients without any risk factors or associated symptoms, and physical precipitating events; (iv) vascular risk factors.

First, the analysis of the patients' medical data, including vascular risk factors and a history of migraine, supplied fresh clues to the aetiological mechanism of TGA. It showed that vascular risk factors, namely HBP and hypercholesterolaemia, cannot be used to characterize patients and form an isolated cluster. These results are in accordance with the aetiological assumptions made by Hodges and Warlow (1990a) and confirm the lack of association between TGA and vascular risk factors. Moreover, no relationship was observed between a history of migraine and headache occurring during an episode of TGA, suggesting that they arise from two distinct mechanisms. Indeed, headache may be symptomatic of an acute and transient episode as it was also observed in our control group.

Secondly, the HCA results revealed three clusters that capture at least three prototypical but non-exclusive groups reflecting probable TGA variants. The first cluster associated the emotional variables, that is, the pathological personality (personality disorder and anxiety traits) with women. The second cluster gathered men with the variables representing an absence of medical history, an absence of associated symptoms and the physical precipitating events. The third cluster linked a history of migraine with the younger patients. On the basis of these three emerging profiles, we suggest that TGA may result from a variety of physiopathological mechanisms according to the nature of the patient.

General discussion

This work is an original survey of the demographic and clinical features of TGA, based on a review of the literature and the thorough study of 142 personal cases. It clearly validates Hodges and Warlow's findings/criteria, as our data confirm that TGA frequently occurs in 60-year-olds and that the episode occurs mainly in the morning and lasts ~6 h. As has been previously reported, the attack is often associated with headache, dizziness and nausea. Results concerning age, number of attacks, duration, time of onset and associated symptoms match those in the literature. Among these features, some are important for the diagnosis. Unlike the epileptic form of amnesia, TGA rarely lasts <1 h, and recurrences remain exceptional. Consequently, the duration and number

of attacks represent relevant variables, especially when it comes to distinguishing TGA from transient epileptic amnesia (Warlow *et al.*, 2001).

Our investigation also allowed us to assess the role of vascular and migraine risk factors in TGA. The results of the classification suggest that vascular risk factors such as HBP and hypercholesterolaemia were not related to any of the patient groups. Conversely, they suggest that migraine may represent a risk factor for triggering TGA in younger patients (<56 years old). As has already been hypothesized by some authors, who found a higher frequency of migraine in TGA patients than in age-matched controls, these data suggest the involvement of migraine in the pathogenesis of this syndrome.

Lastly, our results emphasize the usefulness of the psychological investigation, as they suggest a role of personality disorders, and a history of anxiety/depression in TGA patients, especially women. Moreover, the association of a psychological personality disorder with the presence of emotional precipitating events gives some clues that may help us to understand the aetiology of TGA more clearly (Inzitari *et al.*, 1997). With this study, we have highlighted the involvement of emotional and psychological variables in TGA, and have indicated the value of a systematic investigation in future studies. Moreover, given the small number of controls, it would be particularly relevant to pursue the exploration of the psychological features in performing a specific case–control study and using specific psychological tools.

In conclusion, as TGA is a neurological syndrome exclusively defined by clinical features, a wide-ranging survey of the clinical characteristics commonly observed in TGA, as well as those more rarely described, appeared essential. Moreover, by performing an additional analysis of our population using new techniques, we have demonstrated that TGA may refer to at least three different groups of patients. According to these results three interpretations concerning the physiopathological significance of the classification might be expressed. First, we might speculate on one single mechanism

at the root of the different forms of TGA. As in post-traumatic stress disorder, acute stress and some forms of non-amnesic traumatic brain injury (Bremner, 1999; Joseph and Materson, 1999), this mechanism may be neurotoxic and affect the hippocampal function. It might occur after emotional or physical stress. Secondly, another hypothesis is based on the recent data using duplex sonography or diffusion-weighted imaging and suggests that in some cases TGA may occur after a venous congestion in the context of insufficient jugular-vein valves and precipitating Valsalva manoeuvre (Sander and Sander, 2005). According to our results, this mechanism may be specific to one group of patients gathering men with physical precipitating events. Thirdly, for the group highlighting the association between younger patients and past migraine history, we may speculate on neurochemical mechanisms such as the spreading depression possibly involved in migraine. However, since young people have a higher risk of experiencing migraine in comparison with older people, we cannot exclude the simple co-occurrence of TGA in these young patients.

In distinguishing several groups of patients, this work suggests that TGA may refer to a single expression of several physiopathological phenomena. However, this analysis does not exclude the fact that some individual patients may well fall out of these prototypical groupings. One of the interesting goals of future research would be to test this model using neuroimaging techniques.

Acknowledgements

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Appendix
References analysed in the present article
Group studies

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Case reports

Asada *et al.*, 2000; Ay *et al.*, 1998; Beauregard *et al.*, 1997; Berlit, 2000; Bucuk *et al.*, 2004; Bonnet *et al.*, 2004; Budson *et al.*, 1999; Danek *et al.*, 2002; Dang and Gardner, 1993; Evans *et al.*, 1993; Evers *et al.*, 2002; Felix *et al.*, 2005; Freeman, 1993; Gass *et al.*, 1999; Goldenberg *et al.*, 1991; Goldenberg, 1995; Härting and Markowitsch, 1996; Hodges, 1994; Jia *et al.*, 2002; Jovin *et al.*, 2000; Jung *et al.*, 1996; Kapur *et al.*, 1996; Kazui and Tanabe, 1995; Kettaneh *et al.*, 2001; LaBar *et al.*, 2002; Laloux *et al.*, 1992; Lane, 1997; Lin *et al.*, 1993; Litch and Bishop, 2000; Litch and Bishop, 1999; Mahmoud and Elizabeth, 1996; Marinella, 2004; Masson *et al.*, 1992; Matsuda *et al.*, 1993; Matsui *et al.*, 2002; Merriam *et al.*, 1992; Mizuno-Matsumoto *et al.*, 2001; Okura *et al.*, 1996; Pradalier *et al.*, 2000; Saito *et al.*, 1997; Sakashita *et al.*, 1997; Sakashita *et al.*, 1993; Savitz and Caplan 2002; Schiefer and Sparing, 2005; Schmidtke *et al.*, 1988; Stippich *et al.*, 2000; Stracciari, 2003; Takeuchi *et al.*, 2004; Takeuchi *et al.*, 1998; Tanabe *et al.*, 1991; Warren *et al.*, 2000; Zorzon *et al.*, 1998.

References of studies performed in our laboratory including personal cases

Baron *et al.*, 1994; Eustache *et al.*, 1997; Eustache *et al.*, 1999; Guillery *et al.*, 2000; Guillery *et al.*, 2001; Guillery *et al.*, 2002; Quinette *et al.*, 2003; Guillery-Girard *et al.*, 2004; Guillery-Girard *et al.*, 2006.