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ORIGINAL ARTICLE

A study of right-left shunt in transient global amnesia

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Abstract
Introduction: Transient global amnesia (TGA) is a disorder of unknown aetiology. In recent studies, TGA was associated with a right to left shunt (RLS). We studied the presence of the RLS in patients with TGA and we compared this series with patients who had suffered a transient ischaemic attack (TIA).
Patients and methods: We included 66 consecutive TGA patients. In these patients a transcranial Doppler was performed to determine the presence of a RLS. We collected data on the TGA episode, vascular risk factors, migraine history, recurrence of TGA and neuroimaging in patients with and without RLS. We compared the prevalence of the RLS in TGA series with 59 patients with TIA.
Results: The prevalence of RLS was 21.2% in patients with TGA. The RLS was associated with the migraine history (40% versus 13%; p=0.014) and a Valsalva manoeuvre as a triggering factor (50% versus 14.5%; p=0.022). A greater prevalence of RLS was detected in patients with TIA (55.9% versus 21.2%; p<0.001).
Conclusions: The RLS prevalence in TGA patients is similar to the general population but significantly lower than the prevalence in TIA patients. The association with a Valsalva manoeuvre as a precipitating factor in the TGA patients with RLS could play a role in the aetiopathogenesis of the TGA.

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PALABRAS CLAVE
Amnesia global transitoria;
Shunt derecha-izquierda;
Foramen oval permeable;
Maniobra de Valsalva;
Ataque isquémico transitorio

Estudio de *shunt* derecha-izquierda en la amnesia global transitoria

Resumen
Introducción: La amnesia global transitoria (AGT) es una entidad de etiopatogenia incierta. En recientes estudios se cita la posible asociación entre la AGT y el *shunt* derecha-izquierda (SDI). Por ello estudiamos la presencia de SDI en una serie de pacientes con AGT de nuestra población y la comparamos con otra población de pacientes con ataque isquémico transitorio (AIT).
Pacientes y métodos: Recogimos de forma consecutiva 66 pacientes con AGT en los que se realizó un estudio de SDI mediante Doppler transcraneal. Comparamos las características clínicas del episodio, los factores de riesgo vascular, el antecedente de migraña, la recurrencia de AGT y la neuroimagen entre las AGT con y sin SDI. Comparamos la prevalencia de SDI con la de una serie de 59 casos de AIT de origen indeterminado.
Resultados: En el grupo de AGT la prevalencia de SDI fue del 21,2%. La presencia de SDI se asoció con el antecedente de migraña (el 40 frente al 13%; p = 0,014) y una maniobra de Valsalva como factor desencadenante (el 50 frente al 14,5%; p = 0,022). Se observó una mayor frecuencia de SDI en el grupo de AIT (el 55,9 frente al 21,2%; p < 0,001).
Conclusiones: La prevalencia de SDI en los pacientes con AGT es similar a la descrita en la población general, pero significativamente inferior a su prevalencia en aquellos con AIT de origen indeterminado. La asociación con una maniobra de Valsalva como desencadenante del episodio en las AGT con SDI podría implicar un mecanismo etiopatogénico en este subgrupo.

Introduction

Transient global amnesia (TGA) is defined as a disorder of both anterograde and retrograde memory, of sudden onset and recovery within 24 h, which leaves a mnemonic gap of the episode as the only sequel[1]. Its diagnosis requires ruling out head injury, epileptic seizure and focal neurological signs in a neurological examination.

To date, various aetiopathogenic mechanisms[2] have been proposed for this disorder (migraine, epilepsy, arterial ischemia, venous congestion), but its aetiology is still unknown. Neuroimaging studies have recently shown reversible changes in the hippocampus of these patients, which raises the possibility that metabolic stress could be the trigger of the TGA episode, rather than a classic arterial ischemia[3,4].

Previous studies investigated the classic vascular risk factors in patients with TGA and obtained discordant results[5,6]. Patients with and without episodes of TGA were also compared; there were no differences between them with respect to these vascular risk factors[7].

Following the vascular hypothesis, Klotzsch et al.[8] were the first to link TGA with right-to-left shunt (RLS); 55% of patients in the population with TGA studied presented RLS, compared with 27% of the general population. This association was not reproduced in subsequent studies[9].

For the above reasons, we decided to carry out a study of the prevalence of RLS in patients with TGA compared with a population of patients with TIA. In addition, we looked for the possible existence of clinical or radiological features distinguishing patients with TGA and RLS.

Patients and methods

We prospectively collected data from patients referred to our hospital outpatient clinics with the diagnosis of TGA, from January 2004 to December 2006, who met the Caplan criteria amended by Hodges[1]. On the first visit, we collected a detailed medical history including history of smoking, alcoholism, vascular risk factors, migraine (according to the HIS classification) and cerebrovascular disease, as well as clinical features of the episodes (trigger factors, duration, symptoms associated with memory loss). It should be pointed out that, when defining the Valsalva[10] manoeuvre variable, we included all those patients who, in addition to presenting a pure Valsalva manoeuvre as a trigger, also reported as a causal factor a situation in which it was very likely that this might have occurred, such as sexual intercourse or strenuous physical exercise.

We conducted a neuroimaging exploration (computed tomography or magnetic resonance) and an electroencephalogram on all our patients, to exclude secondary causes of TGA. With respect to neuroimaging scans, we defined the variable "chronic injury", referring to the discovery of old cerebral infarctions in the exploration. We also carried out an analysis including haemogram, coagulation and electrolytes, along with liver, renal and lipid profiles, chest radiograph and electrocardiogram.

To study the presence or absence of RLS, all our patients underwent a transcranial Doppler scan with a single-channel device, equipped with a 2 MHz probe (TCD 100M, Spencer Technologies, Multidop DWL). For this purpose, patients were injected with a solution of 9 ml of saline and 1 ml of

air. In the absence of a shunt between the systemic and pulmonary circulation, the air introduced reached the lungs, where it was exhaled without being detected. If this short-circuit was present, microbubbles passed into the systemic circulation and their presence could be detected as embolic signals in the Doppler spectrum of the velocity pattern of the middle cerebral artery. This measurement was performed both in the baseline situation and after performing a Valsalva manoeuvre, following the recommendations of international guides[11]. Minimal or mild RLS was defined as fewer than 10 signals, moderate when there were between 10 and 25 signals, and massive RLS when there were over 25. The RLS factor was considered positive when it was moderate or massive. We excluded from the study all patients on whom this exploration was not performed, due to either their refusal or the lack of a transtemporal opening[11-14].

All patients in whom a RLS was detected underwent an echocardiogram to confirm the patent foramen ovale, as it is the leading cause of RLS in the general population. This ruled out other anatomical alterations such as interatrial septal defect as a cause of the shunt.

In our study, cerebral infarction was defined as a focal neurological deficit of sudden onset lasting more than 24 h and/or associated to an alteration in the compatible neuroimage. The term TIA referred to a focal neurological deficit lasting less than 24 h[15].

During the same period, we collected a population of 59 patients in the neurovascular unit of our hospital who presented a TIA of undetermined origin in spite of having carried out a complete aetiological study. Additionally, TIAs of undetermined origin were excluded if two or more causes coexisted. All these patients underwent the same study protocol as patients with TGA for the study of RLS. The reason for this choice was the clinical similarity between TGA and TIA, since both entities are clinically characterised by presenting a focal neurological alteration lasting less than 24 h and without a cause than can be demonstrated in complementary explorations.

Statistical analysis

The statistical analysis was performed using SPSS 12.0 for Windows (SPSS 12.0 Inc., Chicago, USA). For the comparison of categorical variables, we used the χ^2 test or the Fisher exact test when necessary. Student's t-test, or the Mann-Whitney U test when necessary, was used in the comparison of averages of continuous variables. Continuous variables were expressed as average±standard deviation and categorical variables as n (%). A level of significance <0.05 was considered statistically significant.

Results

Descriptive analysis

A total of 70 patients with TGA were collected, of which 66 were included in the study. The remaining 4 patients were excluded due to the inability to perform a transcranial Doppler study from lack of transtemporal opening.

The study population had an average age of 65.44±7 years; 60% were women. The presence of RLS was demonstrated in 14 patients (21.2%). The demographic characteristics of both groups are listed in table 1.

With respect to the TIA population, the average age was 53.78±11.54 years; 49% were women. The presence of RLS was demonstrated in 33 patients (55.9%). The remaining results are shown in table 1.

Table 1 Descriptive study

	TGA (n=66)	TIA (n=59)	P
Age (years)	65.44±7.1	53.78±11.57	<0.001
Males	29 (39.4%)	30 (50.8%)	0.19
Anxiety disorder	28 (42.4%)	NAV	
Smoking	15 (22.7%)	15 (25.4%)	0.72
Alcoholism	7 (10.6%)	NAV	
Migraine	20 (30.3%)	11 (21.2%)	0.26
Migraine with aura	5 (31.3%)	NAV	
Prior TGA	14 (21.2%)	NAV	
HT	27 (40.9%)	10 (16.9%)	0.003
Dyslipidemia	25 (37.9%)	20 (33.9%)	0.64
Diabetes mellitus	3 (4.5%)	6 (10.2%)	0.22
Ischemic heart disease	7 (10.6%)	3 (5.1%)	0.33
Atrial fibrillation	1 (1.6%)	0	0.8
Cerebral infarction and/or TIA	3 (4.5%)	8 (13.6%)	0.03
Trigger factor	35 (53.8%)	NA	

TGA: transient global amnesia, TIA: transient ischemic attack; HT: hypertension; NA: not applicable, NAV: not available.

Analysis of patients with TGA and RLS compared with those with TGA and no RLS (table 2)

When analyzing the two groups separately, we noted that the presence of RLS was associated with a history of migraine (40 compared to 13%; p=0.014). If we differentiated patients with migraine with aura and without aura, the presence of RLS was also more frequent in those who referred migraine with aura (60 compared to 36.4%; p=0.6), although without reaching statistical significance.

Analyzing the characteristics of the amnesic episode in those subgroups, we observed differences only in terms of a Valsalva manoeuvre as a trigger factor (50 compared to 14.5%; p=0.02).

There were no statistically significant differences regarding history of cerebrovascular disease, chronic cerebral infarction in neuroimaging scans or leukoaraiosis.

Of the patients with RLS, 9 presented moderate RLS and 5, massive. The analysis of these subgroups showed the same trends as the analysis of the group of patients with RLS, but without reaching statistical significance. This was probably due to the small number of patients in each subgroup.

Comparison of patients with TGA and TIA of undetermined origin (table 3)

The population of patients with TGA was significantly older (65.44 compared to 53.78 years; p<0.001) and had a higher prevalence of hypertension (40.9 compared to 16.9%; p = 0.03). Patients with TIA of undetermined origin presented a higher RLS prevalence (55.9 compared to 21.2%; p<0.001), as well as a higher prevalence of patent foramen ovale (PFO) (57.6 compared to 22.2%; p=0.009) and interatrial septal aneurysm (ASA) (37.3 compared to 11.1%; p=0.036).

As for the frequency of cerebral vascular disease, history of TIA or cerebral infarction was more common in patients with TIA of undetermined origin than in patients with TGA (13 compared to 3%; p=0.45). Nevertheless, this was not the case with the presence of chronic lesions in neuroimaging (13.6 compared to 16.7%; p=0.78), probably because the population of patients with TGA was older and asymptomatic vascular lesions are observed in such patients more frequently.

Comparison of patients with TGA and RLS and those with TIA and RLS (table 4)

Focusing on the subgroups of TGA and TIA who presented RLS, we observed the same results as in the preceding paragraph. The only exception was that, in the subgroup of patients with RLS, the history of migraine was more frequent in those with TGA than in those with TIA of undetermined origin (57.1 compared to 20.7%; p=0.02).

Discussion

The prevalence of RLS in our population of patients with TGA is of 21.2%. This prevalence is similar to that of the general population, according to various epidemiologic studies[16-18].

Analyzing the differences between patients with TGA and RLS and patients with TGA without RLS, we noted, firstly, the association of RLS with a history of migraine. This finding

Table 2 Patients with transient global amnesia and right-to-left shunt [TGA RLS (+)] versus those with TGA lacking RLS [TGA RLS (—)]

	TGA RLS (+) (n=14)	TGA RLS (—) (n=52)	p
Age (years)	63.29±7.06	66.02±7.07	0.2
Males	7 (26.9%)	19 (73.1%)	0.36
Anxiety disorder	9 (32.1%)	19 (66.7%)	0.62
Smoking	3 (21.4%)	12 (23.1%)	0.89
Alcoholism	1 (7.1%)	6 (11.5%)	0.63
Migraine	8 (57.1%)	12 (23.1%)	0.014
Migraine with aura	3 (60%)	2 (40%)	0.59
Prior TGA	2 (14.3%)	12 (19.2%)	0.67
HT	6 (42.9%)	21 (40.4%)	0.87
Dyslipidemia	6 (42.9%)	19 (36.5%)	0.66
Diabetes mellitus	0	3 (5.8%)	1
Ischemic heart disease	1 (7.1%)	6 (11.5%)	1
Atrial fibrillation	1 (7.1%)	0	0.22
Cerebral infarction	0	2 (3.8%)	1
TIA	0	0	1
Trigger factors	9 (69.2%)	26 (50%)	0.21
Emotional stress	3 (23.1%)	10 (19.2%)	0.76
Bath	1 (7.7%)	4 (7.7%)	1
Valsalva	5 (38.5%)	5 (9.8%)	0.022

TIA: transient ischemic attack; HT: hypertension.

Table 3 Transient global amnesia (TGA) versus transient ischemic attack (TIA)

	TGA (n=66)	TIA (n=59)	p
Age (years)	65.44±7.1	53.78±11.57	<0.001
Males	29 (39.4%)	30 (50.8%)	0.19
Smoking	15 (22.7%)	15 (25.4%)	0.72
Migraine	20 (30.3%)	11 (21.2%)	0.26
Hypertension	27 (40.9%)	10 (16.9%)	0.003
Dyslipidemia	25 (37.9%)	20 (33.9%)	0.64
Diabetes mellitus	3 (4.5%)	6 (10.2%)	0.22
Ischemic heart disease	7 (10.6%)	3 (5.1%)	0.33
Cerebral infarction and/or TIA	3 (4.5%)	8 (13.6%)	0.03
Right-to-left shunt	14 (21.2%)	33 (55.9%)	<0.001
Patent foramen ovale	14 (21.2%)	34 (57.6%)	0.009
Interatrial septal aneurysm	2 (11.1%)	22 (37.3%)	0.04
Chronic lesions in neuroimage	7 (16.7%)	8 (13.6%)	0.78

Table 4 Transient global amnesia (TGA) and right-to-left shunt (RLS) versus transient ischemic attack (TIA) and RLS

	TGA RLS (n=14)	TIA RLS (n=33)	p
Age (years)	63.29	52.67	0.003
Males	7 (50%)	16 (51.5%)	0.92
Smoking	3 (21.4%)	10 (30.3%)	0.53
Migraine	8 (57.1%)	6 (20.7%)	0.02
Hypertension	8 (42.9%)	5 (15.2%)	0.04
Dyslipidemia	6 (42.9%)	10 (30.3%)	0.41
Diabetes mellitus	0	5 (15.2%)	0.3
Ischemic heart disease	1 (7.1%)	2 (6.1%)	1
Cerebral infarction and/or TIA	0	4 (12.1%)	0.3
Patent foramen ovale	4 (40%)	24 (72.7%)	0.06
Interatrial septal aneurysm	2 (20%)	14 (42.4%)	0.2
Chronic lesions in neuroimage	0	4 (12.1%)	0.25

is consistent with previous studies carried out on this subject, which already showed this association[19-22]. Likewise, the relationship with migraine with aura in our patients is more common, despite not reaching statistical significance. This is probably because of the small number of patients in our series who had that background.

According to several studies, migraine increases the risk of ischemic cerebral events slightly[23-25], although the pathogenic mechanism has not been adequately established so far. At the present moment, there is no certainty about the potential role of PFO.

In this sense, the work of Klotzsch et al.[8] is very interesting, because it generates the same assumptions as to whether the presence of RLS, and therefore of PFO, could be the cause of TGA; they could be caused by either an embolic mechanism, as might be the case for cerebral infarctions, or by allowing the passage of toxic substances that escaped the pulmonary filter to the neurons of the hippocampus. However, so far the relationship between RLS and TGA has not been reproduced in either the study by Maalijkjy et al.[9] or in ours.

Analyzing the results in more detail, we observe the association of RLS with the Valsalva manoeuvre as a trigger factor of TGA. This could raise the hypothesis that this manoeuvre could have a role in the aetiopathogenesis of TGA, at least in the subgroup of patients with RLS, given that the pressure in the right chambers of the heart is increased during these manoeuvres and, therefore, so is the magnitude of the shunt. It has recently been suggested that the incompetence of the jugular veins may have an important role in the aetiopathogenesis of TGA[26-28]. This finding could be included in this line, because there is an increase in intrathoracic pressure during the performance of a Valsalva manoeuvre that facilitates the failure of the jugular veins.

When comparing the population of patients with TGA with that of patients with TIA of undetermined mechanism, it was observed that the age of the patients with TGA was higher than that of patients with TIA. This probably also explains why the frequency of hypertension is greater among patients with TGA. The remaining vascular risk factors and heart diseases had the same frequency in both groups.

The frequency of RLS was significantly higher among patients with TIA than among patients with TGA, which supports the hypothesis that these entities have different pathogenic mechanisms. In addition, the history of cerebrovascular disease was more frequent among patients with TIA. Several studies have shown that the risk of suffering a new vascular event is higher among patients with TIA than among patients with TGA[6,29], although it is true that the recurrence of a TIA of undetermined origin is lower than in those of known aetiology, mainly atherothrombotic and lacunar[30,31]. Recent neuroimaging studies also support the pathophysiological difference between TIA and TGA[3,4]. All this makes it seem unlikely that there is an aetiopathogenic relationship between TIA and TGA.

In conclusion, it should be emphasised that the prevalence of RLS in patients with TGA was similar to that of the general population in our study, except in the subgroup of patients in whom TGA was triggered by a Valsalva manoeuvre. It is possible that RLS could have a determinant role in the pathogenesis of this entity in these patients. Furthermore, RLS prevalence was much higher among patients with TIA, which represents more data against the ischemic hypothesis as the aetiology of TGA.

Presentations

Part of this study was presented as an oral communication at the LVII Meeting of the Spanish Society of Neurology.

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Conflict of interests

The authors declare no conflict of interests.

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