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ORIGINAL COMMUNICATION

Is transient global amnesia a risk factor for amnestic mild cognitive impairment?

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Abstract Transient Global Amnesia (TGA) is a common condition of unknown aetiology characterised by the abrupt onset of severe anterograde amnesia, which lasts less than 24 hours. Some authors have suggested that subclinical impairment of memory functions may persist for much longer, but neuropsychological assessment lasting years after TGA attack has not been performed so far. The aim of this study was to evaluate long-term cognitive functions in patients with a previous TGA episode. Fifty-five patients underwent a standardised neuropsychological assessment after at least one-year from the TGA attack, and were compared with 80 age-matched controls. TGA patients showed worse performances on tests evaluating verbal and nonverbal long-term memory and attention, with comparable global cognitive functions. By applying current criteria for amnestic Mild Cognitive Impairment (MCI-a) on TGA subjects, a group consisting of 18/55 (32.7 %) MCI-a subjects was identified. There was no association between the presence of MCI-a and demographic variables, vascular risk factors, years since the TGA episode, or ApoE genotype. This study demonstrates that TGA appears to be a relatively benign syndrome although objective memory deficits fulfilling MCI-a criteria persist over time, as detected by multidimensional neuropsychological tasks performed at long-term follow-up.

Key words transient global amnesia (TGA) · mild cognitive impairment (MCI) · cognitive functions

Introduction

Transient Global Amnesia (TGA) is a common condition of unknown aetiology characterised by the abrupt onset of severe anterograde amnesia, repetitive queries, retrograde amnesia and absence of other neurological signs or symptoms [1, 2]. TGA lasts less than 24 hours, being defined as a brief self-limiting event with rapid recovery of memory deficits, and characterized by impairment of long-term episodic memory and sparing of working memory [3].

It has been demonstrated that patients with multiple TGA attacks are impaired on tasks measuring memory and visuospatial abilities compared with patients who suffered from a single TGA episode. Thus, these data suggest that TGA could leave a few subclinical memory deficits that are probably exacerbated by repeated attacks [4].

Some authors have claimed that subclinical impairment of memory functions may persist for much longer, but neuropsychological assessment some years after a TGA attack has not been performed so far [3, 5–7]. To date, it is still unclear whether the supposed hippocampal-diencephalic dysfunction is a transient phenomenon or it is an underlying feature of TGA patients, af-

fecting memory functions over time. These observations fit well with our study, aimed to evaluate cognitive functions of subjects with a previous TGA episode.

Methods

Patients consecutively admitted to the Department of Medical Sciences, Neurology Clinic, University of Brescia, Italy from 1997 to 2003 for an episode of transient loss of short-term memory without impairment of consciousness or remarkably abnormal behaviour were enrolled.

Each subject underwent a clinical and neurological examination, a global neuropsychological assessment, computed tomography and electroencephalography at the onset of symptoms. Only patients who met Caplan's and modified Hodges' and Warlow's criteria for TGA were considered for the study: (1) abrupt onset of inability to retain new information and retrograde amnesia of variable extension; (2) preservation of immediate memory and personal identity without cognitive impairment other than amnesia; (3) evidence provided by a reliable observer who witnessed the episode from the beginning; (4) absence of important accompanying focal neurological signs (only slight asymmetry of the reflexes was allowed) or epileptic features; (5) regression of symptoms within 24 hours except persistent amnesia for the period of the attack; and (6) no epilepsy, psychiatric illness, recent head trauma (in the 72 hours preceding the episode of TGA), progressive mental deterioration, or alcohol or drug abuse in past medical history [1, 8].

Detailed information about the TGA episode was promptly collected from the patient or relatives, and the trigger events related to the TGA attack, the duration of the episode, and comorbidities were recorded. Furthermore, genetic variation at the Apolipoprotein E (ApoE) locus was determined by restriction isotyping using PCR amplification and subsequent digestion with *Hha I* (New England Biolabs) [9].

Only patients who had at least one-year follow-up from the TGA attack were recruited for this study and further evaluated. Then this TGA subgroup underwent a neurological follow-up examination and a detailed neuropsychological re-evaluation, the latter including Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Geriatric Depression Scale (GDS), Rey Complex Figure copy and recall (RFc and RFr), Short Story (SS), Clock's drawing, Digit Span (DS), and Auditory Verbal Learning Test (AVLT). Instrumental Activities of Daily Living (IADL) and Basic Activities of Daily Living (BADL) were investigated as well.

An age-matched control group, made up of spouses and relatives of patients, underwent the same standardised neuropsychological assessment. The diagnosis of amnestic Mild Cognitive Impairment (MCI) in TGA subjects was based on Mayo Clinic criteria: (1) subjective memory complaint; (2) normal activities of daily living; (3) normal general cognitive functioning; (4) abnormal verbal and/or non verbal memory for age; (5) absence of dementia [10].

Comparisons between groups were performed using the Student t-test and Spearman correlation analysis. Statistical significance was assumed at $p < 0.05$.

Results

Seventy-nine TGA patients have been consecutively enrolled (age, mean ± SD = 66.9 ± 7.7, 54 % female). Among these, only patients who had at least one-year neuropsychological follow-up from TGA attack were considered (n = 55, follow-up: 3.2 ± 1.9 years, range: 1–7 years), and were compared with the control group.

TGA patients and controls did not differ in demographic characteristics (see Table 1).

As shown in Table 2, TGA patients showed worse performances on tests evaluating verbal and non verbal long-term memory functions (SS, TGA vs CON, 7.6 ± 3.8 vs 11.4 ± 4.5, $p < 0.0001$; RFr, 10.6 ± 7.1 vs 14.9 ± 7.5, $p < 0.01$), and attention (DS, 3.8 ± 1.3 vs 5.8 ± 1.2, $p < 0.0001$), with comparable global cognitive functions (MMSE, 28.5 ± 2.0 vs 28.6 ± 1.7) and preserved IADL. No ApoE genotype difference between TGA (ApoEε4: 15.2 %) and controls (13.8 %) was found.

By applying current criteria for amnestic MCI (MCI-a), 18 TGA patients with MCI-a were identified (n = 18/55, 32.7 %). There was no association between the presence of MCI-a and demographic variables (age, education, gender), vascular risk factors (diabetes, heart disease, hypercholesterolaemia), years since TGA episode, or ApoE genotype.

Discussion

We have carried out the first study especially designed to examine the cognitive characteristics of patients with a previous attack of TGA that occurred at least one year before our investigation. The long-term follow-up after TGA episode showed the patients to be in good health without behaviour or mood disorders, but complaining of memory disturbances. The principle objective of this

Table 1 Demographic characteristic of TGA patients and control subjects

Variable	TGA	CON	p
number	55	80	–
Age, years	67.0±7.7	68.5±5.7	n. s.
Gender, female %	59.7%	72%	n. s.
Education, years	7.1±3.3	6.6±2.8	n. s.
ApoE genotype, ε4	15.2%	13.8%	n. s.
Duration, h	4.4±3.5	–	–

TGA transient global amnesia patients; *CON* controls; *ApoE* ApolipoproteinE

Table 2 Neuropsychological assessment scores in TGA patients and control subjects

Test	TGA	CON	p
MMSE	28.5±2.0	28.6±1.7	0.81
Rey figure copy	28.9±7.1	29.0±8.1	0.94
Rey figure recall	10.6±7.1	14.9±7.5	0.01
Short Story	7.6±3.8	11.4±4.5	0.0001
Digit Span	3.8±1.3	5.8±1.2	0.0001
IADL, lost	0	0	–

TGA transient global amnesia patients; *CON* controls; *MMSE* Mini Mental State Examination; *IADL* Instrumental Activities of Daily Living

study was to analyse the presence of a clinically undetectable neuropsychological impairment, which the patients seemed to have an insight for. Verbal and nonverbal memory was investigated. This type of memory in TGA patients has been evaluated in previous studies during the episode, or some days after the attack [11, 12].

Neuropsychological examinations made during the acute phase have shown that TGA is a selective disorder of episodic memory (verbal and nonverbal) with no impairment of general cognitive functions [13]. In many reports it has emerged that TGA patients exhibited a complete recovery of memory and other cognitive abilities after the episode, although some authors found abnormalities in some cognitive tests as well afterwards [14].

Our long term follow-up study shows that TGA is associated with both verbal and nonverbal isolated memory impairment, which is still present several years after TGA attack, without having impact on activities of daily living.

Basing on Mayo Clinic criteria, an MCI-a group was defined among TGA subjects [10]. In this group, cognitive impairment is not influenced by either vascular comorbidities, which are common in patients with a transient ischaemic attack, or by ApoE genotype, which is the more widely known genetic risk factor for sporadic Alzheimer disease (AD). Thus, this observation suggests that in subjects with a previous TGA, memory impairment seems to have its own aetiology, due to a specific and chronic involvement of hippocampal-diencephalic structures, not sharing the same origin of vascular cognitive impairment or of the most common neurodegenerative disease, i. e. AD.

This study teaches us that TGA patients present a mild long memory dysfunction in verbal and nonverbal materials independent of other neuropsychological functions. As in all previous studies of this issue, we can not disentangle whether the cognitive deficits result from the attack per-se or they are pre-existent, predisposing to the TGA episode. Further investigations would be required to better understand the pathogenesis of TGA, the factors related to the cognitive deficit, and the possible evolution of the associated amnestic MCI.

References

1. Hodges JR, Warlow CO (1990) Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry 53: 834–843
2. Fisher CM (1982) Transient global amnesia. Precipitating activities and other observations. Arch Neurol 39:605–608
3. Quinette P, Guillery B, Desgranges B, de la Sayette V, Viader F, Eustache F (2003) Working memory and executive functions in transient global amnesia. Brain 126:1917–1934
4. Gallassi R, Stracciari A, Morreale A, Lorusso S, Rebucci GG, Lugaresi E (1993)Transient global amnesia: neuropsychological findings after single and multiple attacks. Eur Neurol 33: 94–298
5. Hodges JR, Oxbury SM (1990) Persistent memory impairment following transient global amnesia. J Clin Exp Neuropsychol 12:904
6. Hodges JR, Warlow CP (1990) The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. Brain 113: 639–657
7. Kessler J, Markowitsch HJ, Rudolf J, Heiss WD (2001). Continuing cognitive impairment after isolated transient global amnesia. Int J Neurosci 106: 159–168
8. Caplan LB (1985) Transient global amnesia. In: Fredericks JAM, ed. Handbook of Clinical Neurology, Vol 1(45). Amsterdam: Elsevier Science 205–218
9. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S (1993) Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 342: 697–679
10. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56:303–308
11. Hodges JR, Ward CD (1989) Observations during transient global amnesia: a behavioural and neuropsychological study of five cases. Brain 112:595–620
12. Kritchevsky M, Squire LR (1989) Transient global amnesia: evidence for extensive, temporally graded retrograde amnesia. Neurology 39:213–218
13. Regard M, Landis T (1984) Transient global amnesia: neuropsychological dysfunction during attack and recovery in two "pure" cases. J Neurol Neurosurg Psychiatry 47:668–672
14. Kritchevsky M, Squire LR, Zousounis JA (1988) Transient global amnesia: characterization of anterograde and retrograde amnesia. Neurology 38: 213–219