Psychiatry Research 176 (2010) 51–54

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Severely stressful events and dementia: A study of an elderly Greek demented population

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ARTICLE INFO

Article history:
Received 13 March 2008
Received in revised form 31 May 2009
Accepted 11 June 2009

Keywords:
Post-Traumatic Stress Disorder (PTSD)
Risk factors
Elderly
Dementia
Stressful events

ABSTRACT

There is evidence that proneness to experience psychological distress is a risk factor for Alzheimer's disease (AD). In the present study, an attempt is made to examine the possible association between stressful events and cognitive impairment of the elderly, based on a sample of 1271 patients (500 male, 771 female) diagnosed with dementia according to the DSM-IV criteria and 140 age- and gender-matched cognitive healthy subjects. All patients were recruited from the Memory and Dementia Outpatient Clinic of the 3rd University Department of Neurology in "G. Papanikolaou" General Hospital, Thessaloniki, and examined over a period of 7 years. The majority of patients reported a history of a stressful event before the onset of dementia ($n=990$, 77.9%), while fewer patients reported insidious onset ($n=281$, 22.1%). The most frequently reported event was the announcement of a life threatening disease ($n=472$, 37.1%), followed by problems within the family ($n=157$, 12.4%), spouse death ($n=100$, 7.9%), death of a sibling or other beloved person ($n=77$, 6.1%). Only 55% of the control subjects encountered stressful events, which is significantly different from the percentage of the study group. Our results demonstrate that a stressful event in the elderly could potentially trigger a cognitive decline.

1. Introduction

Although there are known implications of the way stressful events affect memory and cognition, only a relatively small number of studies have been devoted to the subject. The majority of these studies measured hippocampal volume in patients with Post-Traumatic Stress Disorder (PTSD). The hippocampus, which plays a vital role in memory formation was found to have a smaller volume in people who suffered from PTSD compared with control subjects (Villarreal et al., 2002). Moreover, using MRI scans, Bremner et al. (1995) measured the hippocampal values in 26 Vietnam veterans with PTSD compared with age- and gender-matched healthy controls. They found that the veterans had a significantly smaller (8%) smaller right hippocampal volume in comparison to control subjects, which was associated with short-term verbal memory deficits as measured with the Wechsler Memory Scale. However, no difference in the volume of other brain regions, such as caudate nucleus and the temporal lobe, was found.

In a recent study by Wilson et al. (2003) the cognitive function of elderly Catholic clergy members was examined. All participants underwent annual clinical evaluations, which included clinical classification of AD. At the baseline evaluation, participants completed a measure of the tendency to experience psychological distress, a stable personality trait that served as an indicator of susceptibility to negative emotional states across the life span. More than 90% of participants who died underwent a uniform post-mortem examination of the brain. The association of distress proneness with AD, cognitive decline and measures of AD pathology was examined. During a mean of 4.9 years of follow-up, 140 persons developed AD. Those high in distress proneness (90th percentile) had twice the risk of developing AD than those low in distress proneness (10th percentile). It was concluded that proneness to experience psychological distress is a risk factor for AD, an effect independent of AD pathologic markers such as amyloid plaques and neurofibrillary tangles. Another study (Tsolaki et al., 2003) with 149 orthodox monks and nuns in Greek and Cypriot Monasteries provides further evidence that less stress might not prevent the appearance of dementia, but delays the onset of symptoms.

In a recent French study including 565 patients (Charles et al., 2006), the role of loss, repeated or prolonged stress, psychological trauma and depression-inducing events was examined, and it was found that 79% of responders related the dementia to one or several life events. This study takes into account stress factors ("stressors") but not factors influencing their impact on the subject such as an individual predisposition (genetic, psychopathologic, coping abilities) and social support.

As noted above, the term 'Post-Traumatic Stress Disorder' is widely used to describe a certain psychiatric condition. There are many

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0165-1781/$ – see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.psychres.2009.06.001

studies that have been performed concerning the effect of PTSD on the volume of the hippocampus, suggesting that hippocampal damage might cause memory impairment. Many similarities are observed between PTSD and AD, such as a) the hippocampus is the most vulnerable brain structure, b) the first symptom is memory problems, c) increased levels of glucocorticoids are observed in both conditions and d) women are more susceptible than men in both conditions. However, except for a few studies, no adequate research has been performed on the role of PTSD in the elderly and the relationship of stressful events to the development of dementia.

Table 1
Criteria for differential diagnosis of the several types of dementia.

According to these criteria:
- a. Dementia is established by clinical examination and by a standard test of cognitive function (MMSE, Blessed Dementia Scale) and confirmed by neuropsychological testing.
- b. Significant deficiencies in two or more areas of cognition, for example, word comprehension and task completion ability.
- c. Progressive deterioration of memory and other cognitive functions.
- d. No loss of consciousness.
- e. Onset from age 40 to 90, typically after age 65, and free of other diseases that could produce loss of memory and cognition.

Vascular dementia was diagnosed according to the NINDS-AIREN criteria (Roman et al., 1993).

Lewy body dementia (DLB) was diagnosed according to the criteria of McKeith et al. (1996):
- a. The central feature required for a diagnosis of dementia with Lewy bodies (DLB) is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal–subcortical skills and visuospatial ability may be especially prominent.
- b. Two of the following core features are essential for a diagnosis of probable DLB, one is essential for possible DLB.
  - i. Fluctuating cognition with pronounced variations in attention and alertness.
  - ii. Recurrent visual hallucinations which are typically well formed and detailed.
  - iii. Spontaneous motor features of parkinsonism.
- c. Features supportive of the diagnosis are:
  - i. Repeated falls
  - ii. Syncope
  - iii. Transient loss of consciousness
  - iv. Neuroleptic sensitivity
  - v. Systematised delusions
  - vi. Hallucinations in other modalities.
- d. A diagnosis of DLB is less likely in the presence of:
  - i. Stroke disease, evident as focal neurological signs or on brain imaging.
  - ii. Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture.

Frontotemporal dementia according to the criteria of Neary et al., 1998, which are mentioned in detail below

Core features
- a. Insidious onset and gradual progression
- b. Early decline in social interpersonal conduct
- c. Early impairment in regulation of personal conduct
- d. Early emotional blunting
- e. Early loss of insight

Supportive features
- a. Behavioural disorder
  - ○ Decline in personal hygiene and grooming
  - ○ Mental rigidity and inflexibility
  - ○ Distractibility and impersistence
  - ○ Hyperorality and dietary changes
  - ○ Perseverative and stereotyped behaviour
  - ○ Utilisation behaviour
- b. Speech and language
  - ○ Altered speech output:
    - i. aspontaneity and economy of speech
    - ii. press of speech
  - ○ Stereotypy of speech
  - ○ Echolalia
  - ○ Perseveration
  - ○ Mutism
- c. Physical signs
  - ○ Primitive reflexes
  - ○ Incontinence
  - ○ Akinesia, rigidity and tremor
  - ○ Low and labile blood pressure

Table 2
Number of patients per type of dementia studied.

No	Type of dementia	Number (male)	Percentage (%)
1	Alzheimer's disease (AD)	811 (282)	63.8
2	Lewy body dementia (LBD)	74 (33)	5.8
3	Fronto-temporal dementia (FTD)	185 (76)	14.6
4	Vascular dementia (VD)	121 (71)	9.4
5	Mixed dementia (MD)	80 (38)	6.5
	Total	1271 (500)	100.0

The aim of the current study was to assess the relation between stressful events and the clinical diagnosis of dementia.

2. Methods

2.1. Participants

We examined two groups of subjects: Group A consisted of 1271 patients (500 male, 771 female) diagnosed with dementia according to the DSM-IV criteria (American Psychiatric Association, 1994). Alzheimer's disease was diagnosed according to the criteria of McKhann et al. (1984). The examination took place during a time period of 7 years (1998–2005). Group B consisted of 140 (48 males, 92 females) cognitively healthy subjects. The two groups were age-matched (t-test for independent samples $p>0.05$; two tailed) and gender-matched ($x^2=1.36$, $p=0.24$).

Differential diagnosis was made according to internationally accepted criteria, which are presented extensively in Table 1. The diagnosis was made after careful medical history, physical examination, laboratory testing, neuropsychological tests and brain-imaging scans performed by experienced health professionals (doctors, psychologists). All cases of primary depression were excluded. All patients were recruited from the Memory and Dementia Outpatient Clinic of the 3rd University Department of Neurology in "G. Papanikolaou" General Hospital, in Thessaloniki, Greece. The controls were recruited from a healthy population sample of adult day care centers. The number of patients per type of dementia is shown in Table 2.

2.2. Neuropsychological testing

All patients underwent neuropsychological examination including the Mini-Mental Status Examination (MMSE), the Cambridge Cognitive Examination (CAMCOG), the Functional Rating Scale for Symptoms of Dementia (FRSSD), the Functional-Cognitive Assessment Scale (FUCAS), the Geriatric Depression Scale (GDS), and the Hamilton Rating Scale for Depression.

Healthy participants were examined with the same tests in order to exclude cases of dementia. The MMSE (Folstein (Folstein et al., 1975; Fountoulakis et al., 2000) was used for the screening of dementia. Gender or education did not affect performance in the Greek population probably because the majority (85%) of Greek elderly individuals have low levels of education. However, the MMSE is affected by age, with cut-off scores of 23–24 for ages <75 and 22–23 for ages ≥75. The CAMCOG, which forms part of the CAMDEX interview (Roth et al., 1986; Tsolaki et al., 2000) is a brief neuropsychological battery designed to assess a range of cognitive functions and that contributes to the diagnosis of dementia. Performance on the CAMCOG is affected only by age. the cut-off is 73–74 points for ages <75 and 64–65 points for ages >74.

The Functional Rating Scale for Symptoms of Dementia (FRSSD) (Hutton, 1990) estimates the assessment of daily functioning in 14 activities of daily living. The FRSSD is completed by the caregiver, and high scores represent severe difficulties in daily functioning. A score of 5 to 6 points is considered to be the cut-off between healthy persons and patients with dementia. The Functional-Cognitive Assessment Scale (FUCAS) (Kounti et al., 2006) was used as a screening tool for dementia, since it examines executive function in daily life activities, which is considered to play a critical role in the emergence of the disease. The cut-off for discriminating patients and healthy elderly is 42 points. High scores on the FUCAS reflect severe impairment of executive function in everyday life. Performance is not affected by age, gender or education. The medical history of the patients was also obtained.

The Geriatric Depression Scale (GDS) (Fountoulakis et al., 1999) and the Hamilton Rating Scale for Depression (Hamilton, 1960) scales were used to measure the severity of depressive symptoms. The stressful events were reported by caregivers who were asked, in a standardized way, if their patient underwent any stressful event in the last year before the onset of symptoms. A stressful event was defined as a novel and/or unpredictable event, over which the sufferer must have the feeling of no control (Lupien et al., 2007). The answer was yes or no. If yes, the stress factors were reported in detail, and they were classified as shown in Table 3 after qualitative analysis. Caregivers were asked to define how long after the stressful event the clinical symptoms of dementia appeared. Cases reporting changes earlier than 3 months after the stroke were excluded. The onset of dementia was defined by changes in respect to the previous status of the patients, according to four neuropsychological profiles: progressive amnesic dysfunction, progressive aphasia, progressive visual-constructive dysfunction, and progressive dysfunction of behaviour (Weintraub and Mesulam, 1993).