

Verbal memory impairment in subcortical ischemic vascular disease A descriptive analysis in CADASIL

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Abstract

In the elderly, the high prevalence of Alzheimer's disease neuropathology presents a major challenge to the investigation of memory decline in common diseases such as small vessel disease. CADASIL represents a unique clinical model to determine the spectrum of memory impairment in subcortical ischemic vascular dementia (SIVD). One hundred and forty CADASIL patients underwent detailed clinical, neuropsychological and imaging analyses. The Free and Cued Selective Reminding Test was used as a measure of verbal memory. Forty-four out of 140 CADASIL patients (31.4%) presented with memory impairment according to this test. Eight out of 44 (18.2%) subjects with memory impairment matched the definition of the amnesic syndrome of hippocampal type. While alterations in spontaneous recall were related to the severity of subcortical ischemic lesions, the profile of memory impairment, particularly the sensitivity to cueing was found related to other factors such as hippocampal atrophy.

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1. Introduction

Memory impairment is a key criterion in the diagnosis of dementia. The analysis of memory complaints and performances is mandatory for diagnosis of Alzheimer's disease. Memory dysfunction is also considered as a major diagnostic criterion of vascular dementia (VaD) (American Psychiatric Association, 1994; Lopez et al., 1994; Roman et al., 1993; Wetterling et al., 1993). Even in the recently modified

NINDS-AIREN criteria used to encompass the "subcortical ischemic vascular dementia (SIVD)" subtype, the presence of alterations in memory performances is still required for diagnosis (Erkinjuntti et al., 2000). However, while the global cognitive status or dysexecutive syndrome have been extensively described in SIVD, the exact pattern and complete spectrum of memory deficit related to small vessel disease has been scarcely investigated (Hachinski and Bowler, 1993; O'Brien et al., 2003). In the elderly, the frequent coexistence of degenerative and cerebrovascular lesions renders the delineation of the unique contribution of vascular processes to memory decline particularly difficult (Schneider et al., 2007).

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small artery disease related to NOTCH3 gene mutations on chromosome 19 (Joutel et al., 1996; Tournier-Lasserre et al.,

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1993). The main clinical manifestations of the disease include attacks of migraine with aura, mood disturbances, recurrent ischemic strokes and progressive cognitive decline (Dichgans et al., 1998). CADASIL represents a unique clinical model to investigate the pathophysiology of memory alterations in SIVD (Buffon et al., 2006; Chabriat et al., 1995; Charlton et al., 2006; Davous and Bequet, 1995) for several reasons: (1) cognitive symptoms are detected well before the age of 65 years when they are unlikely to be related to age-related degenerative processes, (2) the cognitive profile in CADASIL is similar to that of sporadic small vessel disease related to vascular risk factors (Charlton et al., 2006), (3) the clinical severity is widely variable among the affected individuals and can reflect different stages of SIVD, and (4) the diagnosis is readily confirmed by genetic testing and/or skin biopsy.

In the present study, we used the Free and Cued Selective Reminding Test (FCSRT), a comprehensive procedure for assessing verbal episodic memory to report the frequency, pattern and main clinical and radiological predictors of memory impairment in a cohort of CADASIL patients (Van der Linden et al., 1993).

2. Subjects and methods

2.1. Subjects

The subjects were included in the study if they met the following criteria: (1) diagnosis of CADASIL confirmed by a genetic test and showing a typical mutation in the NOTCH 3 gene, (2) complete neurological and neuropsychological evaluation, and (3) informed consent obtained from each subject or from a close relative when the subject was too severely disabled to give a written consent. Clinical and demographic data were collected at the time of inclusion with detailed baseline neurological examination including the assessment of presence or absence of cardiovascular risk factors, stroke, transient ischemic attack, migraine with and without aura, depression (evaluated by the Montgomery and Asberg Depression Rating Scale (MADRS): Montgomery and Asberg, 1979 and disability rated using the Rankin Scale and the Barthel Index: van Swieten et al., 1988). A diagnosis of dementia was based on the DSM IV criteria. The study was approved by an independent ethics committee.

2.2. Neuropsychological evaluation and analysis

2.2.1. Assessment of memory performances

Before neurological examination, each patient (or his/her relatives when the patient was unable to answer) was interviewed and asked whether he or she had cognitive complaints.

Memory function was evaluated in all subjects using an explicit verbal memory test, the FCSRT adapted from the Grober and Buschke procedure (Buffon et al., 2006; Van der Linden et al., 1993). This test enables to assess both the encoding, storage and retrieval processes of episodic

memory. It includes multiple tasks to explore these different aspects of memory: encoding task or immediate recall, retrieval (spontaneous or with cues), learning (third free recall–first free recall), consolidation (delayed total recall) and the occurrence of false recognitions and intrusions (Grober et al., 1988; Sarazin et al., 2007; Van der Linden, 2004).

Sixteen words had to be learned with a unique category cue (e.g. fruit). After four items were identified correctly, the card was removed, and *immediate cued recall* was tested by giving the cues again in order to control for encoding. Once a group of four items had been successfully encoded (evidenced by complete immediate recall), the next set of four items was presented. This first phase of the test is done to control the encoding process and provides a score called *immediate recall*. Then, three successive recall trials were performed. Each trial consisted of two parts. First, each subject had to freely recall as many items as possible. Next, an orally presented semantic category (“what was the name of the fruit?”) was provided for those items that were not spontaneously retrieved by the patient. This provided a *free recall score* and a *total recall score*, which was the sum of free and cued recall. This provides three successive scores for the free recall (3 scores of 16 points each) and three other scores for the total recall (3 scores of 16 points each). *The sum of the 3 scores of free recalls and the sum of the 3 scores of total recalls was then obtained ($3 \times 16 = 48$ points for each sum)*. We also defined an *Index of Sensitivity of Cueing (ISC)*, which was determined as: $(\text{total recall} - \text{free recall}) / (48 - \text{free recall})$. When this index is low it reflects an alteration of the storage of information. When it is high, it points toward a defect in retrieval (because cues are frequently needed to retrieve the information). After a 30-min delay, filled by other non-verbal tests, a delayed recall task was performed by the patient with the same procedure of free and cued recall, providing a score for *delayed free recall* and a score for *delayed total recall (DTR = maximal score of 16)*. During the test, the number of *intrusions* (i.e. words absent from the list and falsely “recalled”) was recorded. Finally, 48 words (one by page) were shown to the patient among which he had to recognize the words already learned among new words (*recognition*). *False recognitions* (words absent in the list but recognized in the last part of the test) were then noted.

2.2.2. Other neuropsychological testing

Executive functions were assessed using the subtest of Similarities and Block Design from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), the Trail Making Test B (Reitan, 1955) (TMT-B time) and Wisconsin Card Sorting test (revised version by Nelson) (Nelson, 1976) and the semantic verbal fluency test (Kramer et al., 2002). In addition, to take into account attention and/or motor dysfunction, executive functions were also analyzed in the study as the difference of performances between TMT-B time–TMT-A time (Kortte et al., 2002). Digit span forward was used to assess attention while digit span backwards was used as a

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