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Short Report

Consensus-based recommendations for the management of rapid cognitive decline due to Alzheimer's disease

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Abstract

Introduction: Rapid cognitive decline (RCD) occurs in dementia due to Alzheimer's disease (AD).
Methods: Literature review, consensus meetings, and a retrospective chart review of patients with probable AD were conducted.
Results: Literature review showed that RCD definitions varied. Mini-Mental State Examination scores <20 at treatment onset, vascular risk factors, age <70 years at symptom onset, higher education levels, and early appearance of hallucinations, psychosis, or extrapyramidal symptoms are recognized RCD risk factors. Chart review showed that RCD (Mini-Mental State Examination score decline ≥3 points/year) is more common in moderate (43.2%) than in mild patients (20.1%; $P < .001$). Rapid and slow decliners had similar age, gender, and education levels at baseline.
Discussion: RCD is sufficiently common to interfere with randomized clinical trials. We propose a 6-month prerandomization determination of the decline rate or use of an RCD risk score to ensure balanced allocation among treatment groups.

Keywords: Alzheimer's disease; Definition; Dementia; Rapid cognitive decline; Risk factors

1. Introduction

The cognitive decline of dementia due to Alzheimer's disease (AD) varies between patients, with up to one-third being "rapid decliners," based on a definition of a loss of ≥3 points on the Mini-Mental State Examination (MMSE) score within a period of 6 months [1]. Using a definition of a loss of ≥3 points per year on the MMSE score suggests that about 33.9% patients are rapid decliners [2]. This cognitive decline correlates with loss of functional autonomy and mortality [3]. Some factors predict rapid cognitive decline (RCD), such as moderate dementia at onset of treatment, vascular risk factors, a younger age, a higher level of education [4], early appearance of hallucinations and psychosis or extrapyramidal symptoms [5]. Biological reasons for the variable rate of AD-related dementia progression include pathologic changes in the blood vessels and the

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distribution of pathologic changes between limbic and neocortical structures [6], and possibly also distinct amyloid β structures [7]. Various lines of evidence indicate the impact of genetic biomarkers on the progression of cognitive decline in AD-related dementia [8], whereas it has not yet been established whether RCD occurs more commonly in early onset familial AD [9]. The association between the *APOE* ε4 allele and cognitive decline in patients with AD remains controversial [10–30]. In addition, the presence of the K and A variant alleles of the butyrylcholinesterase gene have been associated with slower cognitive decline in patients with severe AD [31,32]. The cognitive decline rate may increase with baseline severity (baseline MMSE score, 17–28.2) in patients with AD [33–40].

Some attempts have been made to manage patients with RCD due to AD-related dementia clinically; these included optimal use of cholinesterase inhibitors [41] and a management algorithm incorporating intercurrent acute events and re-evaluation of the diagnosis [1]. Both meta-analyses and pool analyses have indicated that patients with RCD achieved greater benefits from rivastigmine and galantamine [42,43]. Previous studies have demonstrated that the risk of RCD in patients with AD treated with ChEIs (donepezil, rivastigmine, or galantamine) was significantly decreased [44,45].

We hypothesized that RCD in AD-related dementia can be demonstrated in a clinical population, and that it may be sufficiently common to interfere with group allocation in randomized clinical trials (RCTs) aimed at disease modification. We tested this hypothesis by conducting a review of previously reported data and by a retrospective chart review.

2. Methods

2.1. Consensus meeting and literature review

The committee for this consensus meeting was established in March 2015 and included 13 neurologists/psychiatrists. Among these experts, 12 were from China (J.J., S.C., Y.J., W.K., D.P., W.W., S.X., Q.G., J.Z., L.W., C.W., and Y.T.) and one from Canada (S.G.). The committee members finalized their opinions on controversial clinical questions using available evidence and experience in a face-to-face meeting and in follow-up electronic communications.

A PubMed search was performed before consensus meetings, which took place in Beijing on April 3, 2015, and Jun 12, 2015, respectively. We identified all English articles from January 1, 1990 to April 3, 2015, that were related to rapid progression of AD. Keywords used for the literature search included "Alzheimer disease," "rapid cognitive decline," "rapid decline," "fast progression," and "fast decliner." Evidence of poor quality related to small sample sizes, poor study design, and subjects with comorbidities was excluded from the material used for this consensus meeting.

2.2. Retrospective chart review

A supplementary retrospective chart review was conducted at the McGill Center for Studies in Aging (MCSA) in July and August 2015, involving 235 patients with probable AD, based on National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria. These patients had baseline MMSE scores of 10 to 26 and a mean follow-up of 2 years ±4 months. All these patients were actively followed at MCSA from 2012 to 2015. Patients were distinguished as mildly or moderately affected, based on baseline MMSE scores of 20 to 26 and 10 to 19, respectively, and the proportion of rapid decliners was calculated for each group. A decline of ≥3 points per year on the MMSE score was used for this analysis, based on the findings of the literature review. Patients were then restratified into slow cognitive decline and RCD groups, and the following potential clinical risk factors were compared: the MMSE score and age at baseline, gender, and level of education. All patients were treated with ChEI during the follow-up period.

2.3. Data analyses

A chi-square test was used to compare the proportion of rapid cognitive decliners in the mild and moderate patient groups. It was also used to compare the slow and rapid decline group in terms of the proportion of male and female subjects, as well as the proportion of patients with a high education level (≥9 years) and patients with a low education level (≤8 years). For age and MMSE score at baseline, the slow and rapid decline groups were compared using a two-tailed *t* test, assuming equal variance.

Statistical analyses were performed using Microsoft Excel 2011 for Mac version 14.6.1 (Microsoft Corporation, Redmond, WA, USA).

3. Results

3.1. Literature review

The literature review showed that studies varied in terms of the definition used for RCD, which may have led to variations in the proportion of patients identified with RCD (Table 1) [1–3,36,46–50]. Moreover, in the literature review, moderate dementia, vascular risk factors, a younger age, higher level of education, early appearance of extrapyramidal signs, and neuropsychiatric symptoms were recognized as risk factors for RCD [1,3].

3.2. Chart review

Using a definition of RCD of a loss of 3 points or more per year on the MMSE score, the MCSA chart review showed a frequency of RCD of 20.1% in mild patients (N = 144) and 43.2% in moderate patients (N = 81; $P < .001$).

MMSE score at baseline was also shown to be lower in the rapid decline group than in the slow decline group. The mean MMSE score at baseline was 21.9 in the slow decline group (N = 161) compared with 19.1 in the rapid decline group (N = 64; $P < .001$). There was no statistically