Age at onset and the disturbance of orientation in Alzheimer's disease

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Abstract:

A recent study of Alzheimer's disease (AD) showed a correlation between the disturbance of orientation for time and place and the hypometabolism in the posterior cingulate cortex. In another study of AD, patients with later age at onset have more severe reduction of regional glucose metabolism in the retrosplenial area. These two findings raise a hypothesis that late-onset AD patients have more severe disturbance of orientation than do early-onset patients. We examined the effect of age at onset on the disturbance of orientation using a large sample of mild-to-moderate AD and multivariate statistics controlling for confounding factors. The disturbances were assessed both by the subtest of the Alzheimer's Disease Assessment Scale (ADAS) as neuropsychological measure and by the subscale of the Clinical Dementia Rating (CDR) as clinical measure. The late- than early-onset patients performed significantly worse on the ADAS orientation subtest, and were rated significantly worse on the CDR orientation subscale. The current results confirmed the hypothesis. The clinical characteristic of late-onset patients present a contrast to those of early-onset patients who are reported to show more profound disturbances of language, attention and visuocognitive functions. The differences between early- and late-onset patients suggest a heterogeneity of AD, and are important to increase the accuracy of early diagnosis and management.

Introduction

A considerable number of studies have examined the impact of age at symptom onset in Alzheimer's disease (AD) on the pattern of cognitive deficits, the rate of cognitive decline, the distribution of regional pathological changes and the emphasis of regional cerebral hypometabolism (see Raskind et al. (1995) for review). We recently reported that early- than late-onset patients have more profound deficits of language [Imamura et al., 1998], attention and visuospatial cognition [Fujimori et al., 1998]. Another study showed that later-onset patients have higher prevalence of psychiatric symptoms [Hirono et al., 1998b]. In the study of cerebral metabolism [Yasuno et al., 1998], early-onset AD patients have more severe reduction of regional metabolism in the fronto-temporo-parietal association cortices, while late-onset patients have more prominent metabolic deficit in

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the retrosplenial area. On the other hand, another study of AD [Hirono et al., 1998a] showed the correlation between the disturbance of orientation for time and place and the hypometabolism in the posterior cingulate cortex. The findings of the last two metabolic studies raise a hypothesis that late-onset AD patients have more severe disturbance of orientation than do early-onset patients.

Only one previous research [Koss et al., 1996] examined the relation between age at onset and disturbance of orientation in AD. They reported that older patients showed higher prevalence of the disturbance than did younger patients. In the present study, we assessed the effect of age at onset on the disturbance of orientation using a large sample of mild-to-moderate AD patients. The disturbance was assessed both by quantitative neuropsychological measure and by clinical rating based on an established caregiver interview. The effects of onset age were examined by multivariate statistics controlling for confounding factors.

Patients and methods

Patients

We recruited 323 patients who were assessed in the Hyogo Institute Hospital for Aging Brain and Cognitive Disorders, Himeji, Japan and met the following inclusion criteria. All the patients had a diagnosis of probable AD based on the NINCDS-ADRDA criteria [McKhann et al., 1984], scored 10 or more on the Mini-Mental State Examination (MMSE) [Folstein et al., 1975], had 6 years or more of educational attainment, and were rated as stage 0.5 (very mild), 1 (mild) or 2 (moderate) for overall dementia severity in the Clinical Dementia Rating (CDR) [Hughes et al., 1982; Morris, 1993]. Each patient underwent a neurological examination, a neuropsychological assessment including the Japanese version of the Alzheimer's Disease Assessment Scale (ADAS) [Mohs et al., 1983; Honma et al., 1992], blood chemistry, an electroencephalogram, a magnetic resonance (MR) brain scan and an MR angiogram. We estimated age at symptom onset using information provided by the nearest reliable caregiver. Using a semi-structured interview, a neurologist or a neuropsychiatrist asked each caregiver to describe the initial cognitive symptom which can not be accounted for the aging. If a cognitive symptom other than memory disturbances was reported, then the interviewer asked the caregiver to confirm the presence or absence of the preceding memory symptom. The patients consisted of 254 females and 69 males. The demographic data of the patients (mean ± SD) were as follows: age at assessment, 73.4 ± 8.0; age at onset, 70.5 ± 8.2; educational attainment, 9.0 ± 2.5 years; symptom duration 34.9 ± 24.0 months. The patients scored a mean of 19.0 ± 3.8 on MMSE and a mean of 22.5 ± 8.5 on ADAS. Thirty-one patients were rated as CDR stage 0.5, 200 patients were rated as stage 1 and 92 patients were rated as stage 2.

Assessment of orientation

We employed the orientation subtest of ADAS for the neuropsychological measure. Each patient was instructed to say current year, month, season, date, day of the week, time, place and accompanying person. The test gives a score of 0-8, and a higher score indicates more severe deficit of orientation. The mean scores in the total patients were 4.0 ± 1.9.

The orientation subscale of CDR [Morris, 1993] was used for the clinical measure. The scale rates each patient's impairment of orientation in daily living as 0 (none), 0.5 (very mild), 1 (mild), 2 (moderate) or 3 (severe) based on the information obtained from reliable caregivers. Nine patients were rated as 0, 14 patients as 0.5, 252 patients as 1, 26 patients as 2, and 22 patients as 3. For the current analysis, each patient was classified as having none-to-very mild, mild, moderate or severe impairment, each of which corresponds to CDR orientation 0-0.5, 1,

2 and 3.

Data analyses

We conducted an analysis of multivariate linear regression to assess the effect of age at onset on the neuropsychological score. The statistical model contained the score of the ADAS orientation subtest as the dependent variable, and age at onset, gender, educational attainment and MMSE score as the independent variables. We conducted an analysis of multivariate correlation to assess the onset-age effect on the clinical ratings of orientation impairment. In the statistical model, the variables consisted of age at onset, gender, educational attainment, MMSE score and the rating of the CDR orientation subscale. These multivariate statistical methods reveal the net effect of age at onset as the partial coefficient after eliminating the effects of gender, educational attainment and severity of overall cognitive disturbance represented by MMSE score.

The statistical procedures were performed with the SAS software package [SAS Institute Inc., 1990]. The overall significance level was set at $p < 0.05$. Each result was assessed with a threshold of $p < 0.05/2 = 0.025$ according to the Bonferroni method for protecting false positives in a multiple comparison.

Results

The analysis of multivariate linear regression showed a significant coefficient for age at onset on the score of the ADAS orientation subtest (standard partial regression coefficient; $\beta = 0.13$, $p < 0.005$). The positive coefficient indicates the higher scores (greater deficits of orientation) in the later-onset patients.

The demographic data and the mean age at onset in the patient groups of none-to-very mild, mild, moderate and severe orientation impairment assessed by the CDR subscale are presented in Table 1. There was a significant partial correlation coefficient between the age at onset and the rating of orientation impairment ($r = 0.19$, $p < 0.001$). The positive coefficient indicates the severer impairment in the later-onset patients.

Discussion

The current results showed that the late-onset patients have greater deficit of orientation than do the early-onset patients. The effect of age at onset was significant after eliminating the effects of gender, educational attainment and severity of overall cognitive deficit represented by MMSE score. Koss et al. (1996) reported the higher prevalence of orientation disturbance in

Table 1. The characteristics of each patient group with different severity of orientation impairment.

	None-to-very mild	Mild	Moderate	Severe
Gender (female / male)	16 / 7	196 / 56	22 / 4	20 / 2
Educational attainment (year)	9.2 ± 2.9	9.1 ± 2.5	8.0 ± 2.0	8.4 ± 1.9
MMSE score	22.6 ± 2.7	19.1 ± 3.7	16.2 ± 2.8	17.2 ± 3.4
Age at assessment	68.8 ± 9.6	73.2 ± 8.1	76.8 ± 5.9	76.6 ± 3.6
Age at onset	66.5 ± 9.6	70.3 ± 8.3	73.7 ± 6.5	73.6 ± 3.5

Data are presented as mean ± SD

later-onset patients with mild to moderate AD. Our study delineated the onset-age effect on the severities of orientation impairments.

One possible explanation of the results is the effect of aging. Patients' responses to the question for current year, date and so on may be influenced by their impairment of memory as well as orientation. The ability of memory in later-onset patients, who have older age at assessment, may be reduced by aging. To resolve this issue, we employed the CDR subscale as the clinical measure of the study. The scale rates a patient's impairment only in relation to the patient's premorbid performance, not to that of the general population [Hughes et al., 1982]. The effect of aging is thought to affect the premorbid performance of later-onset patients because they are already old at the disease onset. We thus believe that the aging effect in each patient is eliminated on the rating of orientation impairment. The CDR is reported to have 94 % of specificity and 95 % of sensitivity for screening dementia in aged population [Juva et al., 1995]. This fact suggests that the CDR is robust for the aging effect in older subjects.

The current results and our previous findings [Fujimori et al., 1998; Hirono et al., 1998b; Imamura et al., 1998; Yasuno et al., 1998] delineate a double dissociation in AD: early-onset patients have a more profound reduction of regional metabolism in the association neocortices and show more profound disturbances of language, attention, visuoconstructional ability and visuospatial function. On the other hand, late-onset patients have a more prominent metabolic deficit in the paralimbic area, show more severe disturbance of orientation, and show a higher prevalence of psychiatric symptoms. There may be early- and late-onset neurobehavioral subtypes, which we believe important in diagnosis, evaluation, management and clinical research in AD.

The difference between early- and late-onset patients also raises a possibility of neurobiological heterogeneity of AD. The studies of molecular genetics showed the presence of two or more different genetic factors in familial and sporadic AD, such as a genetic abnormality on chromosome 14, mutations in the gene for amyloid precursor protein on chromosome 21, and the apolipoprotein $\varepsilon 4$ allele (see Harvey and Rossor (1995) and Hyman (1996) for review). The reduction of β amyloid$_{(1\text{-}42)}$ in the cerebrospinal fluid, a biochemical marker of AD, is recently reported to be greater in early- than late-onset patients [Andreasen et al., 1999]. There may be some genetic or neurobiological abnormalities associated with early- and late-onset AD. Further studies are necessary to resolve this issue.

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