

Association between Soft Neurological Signs and Clinical Progression in Alzheimer's Disease

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Abstract

Objective: Unlike cognitive function, clinical assessment of neurological deficits in Alzheimer's disease has received limited attention. This study aimed to determine the association between soft neurological signs and rate of clinical progression in Chinese people with Alzheimer's disease.

Patients and Methods: 104 Chinese patients with late-onset Alzheimer's disease were followed up for an average of 22.5 months (SD, 5.2 months). Soft neurological signs were evaluated with the Cambridge Neurological Inventory. Outcome was determined by deterioration in Clinical Dementia Rating and mortality.

Results: Motor coordination, sensory integration, and failure of suppression signs were more prevalent in participants with Alzheimer's disease than in controls without dementia ($p < 0.001$) and the scores for these signs were significantly correlated with most cognitive function tests ($p < 0.05$). Patients with stable Clinical Dementia Rating scores at follow-up had lower scores for parkinsonian signs ($p < 0.005$) than those who had died during the follow-up period.

Conclusions: The findings suggest that cortical soft neurological signs such as motor coordination and sensory integration, which were highly associated with cognitive performance in patients with Alzheimer's disease, represent overlapping clinical dimensions. The presence of subcortical extrapyramidal signs may signify poorer prognosis.

Key words: Alzheimer's disease, Neurobehavioural manifestations, Neurological diagnostic techniques, Prognosis

Introduction

Alzheimer's disease (AD) is the commonest dementia worldwide. In a recent review of the prevalence of dementia in China, it was estimated that the prevalence rate of AD for people aged 60 years and over was 1.26%.¹ Although progressive cognitive deterioration is central to the diagnosis of AD, the clinical syndrome comprises complex behavioural and neurological manifestations reflecting continuous degeneration of the brain. In people with very

early AD, cognitive deficits are also characterised by impaired delayed recall in episodic memory tests and reduced verbal fluency.²⁻⁵ With increasing cognitive deterioration, patients' ability to evaluate their own cognitive abilities deteriorates. As dementia becomes more severe, very limited cognitive abilities remain and only basic functions are present.

Neurological deficits reflecting cerebral degeneration are not uncommon in patients with AD. With increasing cortical atrophy, neurological signs become more prevalent. Focal neurological signs such as pyramidal signs, which represent localised lesions in the brain, are more commonly found in patients with vascular dementia. However, soft neurological signs (SNS) indicating diffuse damage are likely to be present in AD. The severity of SNS may be indicative of disease progression. The presence of extrapyramidal signs in patients with mild cognitive impairment is associated with a decline in cognitive function and the development of AD.⁶ In established AD, the presence of extrapyramidal signs is also associated with faster cognitive decline, higher mortality, and more severe pathological changes in clinical autopsy studies.^{7,8}

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Despite the presence of significant neurological deficits in patients with AD, the role of clinical neurological examination in the evaluation of AD remains limited. The aim of this study was to identify the pattern of SNS in AD and evaluate its potential clinical significance, particularly in terms of its ability to predict the trajectory of disease progression.

Patients and Methods

The study comprised a 2-year prospective naturalistic study of Chinese patients with AD. At baseline, cross-sectional assessment of cognitive and neurological characteristics was performed. Patients with AD who were referred to a clinic for first psychogeriatric assessment were enrolled in the study. Approximately 2 years after the initial assessment, follow-up evaluation of the cognitive status and severity of dementia was conducted.

Recruitment Centre and Patients

The patients in the study group were recruited from patients whose first assessment was carried out at the psychogeriatric clinic at the Prince of Wales Hospital, Hong Kong. At the time of recruitment, the clinic served most of the New Territories East region of Hong Kong, which had an estimated population of 1.3 million, approximately 11% of whom were older than 65 years.⁹ All participants were recruited between October 2000 and June 2002. For comparison of baseline cognitive and neurological profiles, a control group of age-matched community-dwelling mobile elderly people were recruited from local elderly social centres. The control participants were screened by qualified psychiatrists to ensure that they were cognitively intact and had no previous history of major psychiatric or neurodegenerative disorders.

For inclusion in the study group, all patients had to satisfy the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association criteria for possible and probable AD.¹⁰ To obtain a homogeneous group of patients with AD, only those who were older than 65 at onset were recruited. Patients with a previous history of head injury, significant sensory deficits, unstable physical conditions, or known neurodegenerative and early-onset major psychiatric disorders apart from AD were excluded. To focus on dementia-specific factors that affect deterioration, only patients with mild and moderate AD (Clinical Dementia Rating [CDR], 1 or 2) were recruited.¹¹

The study was approved by the Joint Clinical Research Ethics Committee of the Faculty of Medicine, The Chinese University of Hong Kong, and New Territories East Cluster Hospitals in Hong Kong. Written informed consent was obtained from all patients and/or their first-degree relatives by the attending psychiatrists. The first author or a psychiatrist in the research team was responsible for explanation of the assessment and informed consent. At baseline assessment, patients and/or their caregivers were informed of the proposed second assessment to monitor clinical progress.

After 2 years, an independent consent for follow-up assessment was sought from the patients and/or their caregivers. Clinical progress was assessed only for patients who gave their consent.

Assessment Tools

The severity of AD was evaluated using the CDR.^{11,12} The CDR is a standard instrument for the diagnosis and evaluation of the overall level of severity of dementia. The assessment is based on information obtained through a semi-structured interview with the patient and informant by a trained interviewer. Six areas of functioning are assessed to determine the overall severity of dementia: orientation, memory, community affairs, judgement, hobbies, and personal care. The CDR is divided into 5 stages of severity, ranging from normal cognition to severe dementia. A CDR of 0 represents normal cognition and a CDR of 3 represents severe dementia.

The Mini-Mental State Examination (MMSE) was developed as a pen-and-paper test for the screening of cognitive impairment.¹³ A validated Cantonese version, developed in Hong Kong,¹⁴ was used in this study.

A locally validated Chinese version of the Mattis Dementia Rating Scale (DRS)¹⁵⁻¹⁷ was used to examine the cognitive profiles of patients with AD in this study. The DRS was developed for the assessment of cognitive function in patients with dementia.¹⁶ Besides being a diagnostic tool, the DRS allows sensitive discernment of the degree of severity of AD. The DRS comprises 5 subscales that relate to different cognitive domains: attention, initiation and perseveration, construction, conceptualisation, and memory. A composite score, with a maximum of 144 points, is generated by the summation of the subscale scores.

The Hong Kong List Learning Test (HKLLT) was developed specifically to examine episodic memory function in Hong Kong Chinese people.¹⁸ All participants were read a list of 16 words. This was repeated 3 times so that a learning curve could be generated. Ten minutes later, participants were asked to recall the word list (short-delayed recall). After 30 minutes, the participants were asked to recall the word list again (long-delayed recall). After the long-delayed recall, participants were asked to recognise the word list from a group of words mixed with semantic and phonetic distracters (recognition test).

The Category Verbal Fluency Test (CVFT) has been widely used for the assessment of executive function and as a screening tool for dementia.¹⁹ The CVFT has been used among Chinese elderly people in Hong Kong, and satisfactory psychometric properties have been demonstrated.^{20,21} In the CVFT used in the study, participants were asked to generate exemplars from 3 groups of living objects in 1 minute. The objects included 'animals', 'fruits', and 'vegetables'. The CVFT score represents the total number of exemplars generated in each of the 3 categories. To control for potential differences in their ability to generate exemplars of living and non-living objects, only living objects known to the local elderly people were offered as categories in this test.

The Cambridge Neurological Inventory (CNI)²² was used in this study for assessment of SNS. The CNI is an extended series of neurological tests developed for the assessment of patients with psychiatric disorders, that has been applied to patients with schizophrenia and obsessive-compulsive disorders.²²⁻²⁴ The CNI is divided into 3 main sections. In the first, eye movement disorders, cranial nerves, pyramidal signs, and primitive reflexes are examined. In the second, soft neurological signs (SNS) are assessed. In the third, extrapyramidal signs, involuntary movement disorders, catatonic signs, and gait are assessed. In this study of patients with AD, SNS was the main focus of neurological assessment, as focal neurological signs would be more important in vascular and other non-AD dementia, in which selective cerebral degeneration occurs.

The SNS assessed using the CNI were motor coordination signs, sensory integration signs, primitive reflexes, extrapyramidal signs, and failure of suppression signs. Motor coordination signs were tested using the finger-nose test, finger-thumb tapping, finger-thumb opposition, dysdiadochokinesia, fist-edge-palm test, and the Oseretsky sign. The sensory integration signs examined were extinction, finger agnosia, stereognosia, agraphesthesia, and left-right disorientation. The primitive reflexes assessed were snout reflex, gasp reflex, and palmomental reflex. The dyskinesia signs assessed were simple, complex, and dyskinetic abnormal involuntary movements in the face, trunk, and limbs. The parkinsonian signs included increased tone in the limbs, decreased associated movements in walking, shuffling gait, arm-dropping, tremor, and rigidity in the neck. The failure of suppression signs comprised blinking in saccadic eye movements, inability to wink with one eye, head movement in saccadic eye movement, positive go/no-go phenomenon, and echopraxia. Pyramidal signs were not analysed, as patients with positive pyramidal signs reflecting focal neurological lesions were excluded from the study. For any sign tested, the scoring system was determined as follows: 0, normal; 0.5, questionable; 1, noticeable and mild; 2, definitely abnormal; and signs that were not assessed due to the patient's inability to comprehend instructions were rated as 9. For each patient, scores for each sign tested were combined to give the total score for SNS. Examination of SNS was conducted at the first visit only.

Assessment Schedule

After the baseline evaluation, patients were followed up by their responsible psychiatrists at the psychogeriatric clinics. Treatment suited to the clinical needs of each patient was offered. After 2 years, patients were reassessed for progress of CDR and cognitive function.

Statistical Analysis

Continuous variables were compared using Student's *t* test, categorical data were compared using the Chi squared test, and correlations were analysed using Pearson or Spearman correlations. Non-parametric methods were used when data did not show a normal distribution. A *p* value of 0.05 or less

was accepted as significant. The Bonferroni correction was applied when multiple comparisons were made. For the prospective assessment, patients were classified as 'stable' or 'deteriorated' according to the CDR. Patients with no change in CDR over 2 years were considered stable; those whose CDR had progressed were considered to have deteriorated. Patients who had died prior to follow-up constituted the 'deceased' group. The data were analysed using the Statistical Package for Social Sciences for Windows, version 11.0.

Results

Of the 109 patients initially recruited, 5 were subsequently excluded from analysis due to changes in their physical state and revision of their psychiatric diagnosis. One was found to have carcinoma of the lung shortly after baseline assessment, another was subsequently diagnosed as having delusional disorder, and 3 were found to fit the criteria for mild cognitive impairment at follow-up. As a result, the study population consisted of 104 patients with AD, of whom 82 were women and 22 were men. Their mean age was 78.2 years (SD, 6.0 years; range, 66 to 90 years) and their mean educational level was 3.3 years (SD, 3.9 years). Fifty-seven patients (54.8%) had mild dementia (CDR, 1) and 47 (45.2%) were moderately demented (CDR, 2).

Of the 74 control participants recruited for comparison of neurocognitive profiles, 55 were women and 19 were men. Their mean age and educational level did not differ significantly from those of the patients with AD (Student's *t* test).

Cognitive Profiles

At baseline assessment, the mean MMSE and total DRS scores for patients with AD were 16.2 (SD, 3.7) and 94.9 (SD, 13.7), respectively. For the HKLLT, the mean number of items recalled was 0.27 (SD, 0.9) in the short-delay test and 0.11 (SD, 0.57) in the long-delay test. The mean number of items recognised was 18.2 (SD, 3.1). For the CVFT, the mean number of items recalled in the categories of animals, fruits, and vegetables were 6.5 (SD, 3.3), 6.4 (SD, 2.4), and 6.8 (SD, 2.5), respectively. The mean combined CVFT score was 18.7 (SD, 7.0). There were highly significant differences in the results for all cognitive tests in the control group compared with the AD study population (Student's *t* test, *p* < 0.001).

A comparison of the demographic characteristics of patients with mild AD (CDR, 1) and moderate AD (CDR, 2) revealed that there were no significant differences in age, gender distribution, or educational level (*p* < 0.05). When cognitive profiles of patients with mild and moderate AD were compared, patients with mild AD scored significantly higher in most tests (unpaired *t* test, *p* < 0.001). However, values were not significantly different for long-delay recall in the HKLLT.

Profile of Soft Neurological Signs

The mean baseline scores for the 6 groups of SNS tested and the total SNS score for patients with AD and the con-

trol participants are given in Table 1. There were significant differences between these 2 groups with respect to motor coordination, sensory integration, and failure of suppression signs (Table 1). No primitive reflexes were found in either group, nor were there any significant differences in dyskinesia or parkinsonian signs between the 2 groups (Table 1), which may be related, at least in part, to the very low prevalence of signs in these 2 groups. When the severity of SNS was compared between patients with mild or moderate AD (Table 2), patients with mild AD had significantly lower scores for motor coordination, sensory integration, and total SNS, but not for other groups of signs tested (Table 2).

Correlations between Cognitive Profiles and Soft Neurological Signs

The associations between SNS and cognitive functions were computed using Spearman correlations. Motor coordination signs and total SNS scores showed a significant negative correlation with almost all cognitive domains assessed (Table 3). Sensory integration signs were correlated with the DRS total score and subscale scores for attention, initiation and perseveration, and construction (Table 3). Significant associations between cognitive function and SNS subscale scores for motor coordination and sensory integration remained after post-hoc adjustment for multiple comparisons. Although the severity of parkinsonian signs appeared to be associated with lower total DRS scores and subscale scores for attention and conceptualisation, these trends were not

statistically significant after adjustment for multiple comparisons. There was no significant correlation between dyskinesia and any of the cognitive function test scores.

Baseline Soft Neurological Signs and Follow-up Status

Of the 104 patients evaluated at baseline, 74 (71.2%) were followed up 2 years after the initial assessment. Nineteen (18.3%) had died, 3 (2.9%) had left Hong Kong, and 8 refused reassessment. All deceased patients had died of physical disorders. Of those who were reassessed, 60 (81.1%) were women and 14 (18.9%) were men. The mean interval from baseline assessment to follow-up was 22.5 months (SD, 5.2 months). At follow-up, 29 patients (27.9%) had a CDR of 1, 34 (32.7%) had a CDR of 2, and 11 (10.6%) had a CDR of 3. The CDR of 49 patients (66.2%) was unchanged, 24 patients (32.4%) had deteriorated to the next CDR level, and 1 patient (1.4%) had deteriorated from CDR 1 to CDR 3. There was no significant difference in follow-up interval between those patients whose condition was stable and those who deteriorated; mean values were 22.5 months (SD, 5.1 months) and 22.5 months (SD, 5.5 months), respectively. Patients in the stable group were significantly younger than those in the deceased group at baseline assessment (p = 0.01, one-way analysis of variance with post-hoc comparisons).

Baseline SNS were evaluated in relation to outcome as shown in Table 4. Significant differences in baseline parkinsonian signs were found between the various outcome

Table 1. Baseline scores for soft neurological signs in patients with Alzheimer’s disease and controls.

Soft neurological signs	Alzheimer’s disease Mean (SD)	Controls Mean (SD)	z Score	p Value*
Motor coordination	5.60 (4.69)	2.15 (2.27)	5.48	<0.001
Sensory integration	4.14 (4.86)	1.99 (3.45)	3.76	<0.001
Dyskinesia	0.03 (0.15)	0.06 (0.33)	0.05	>0.05
Primitive reflexes	0 (0)	0 (0)	0	>0.05
Failure of suppression	3.48 (2.62)	1.97 (2.07)	3.94	<0.001
Parkinsonism	0.14 (0.39)	0.15 (0.46)	0.48	>0.05
Total	13.36 (10.09)	6.25 (6.35)	5.18	<0.001

* Indicates significance of difference between the 2 groups, Mann-Whitney U test.

Table 2. Baseline scores for soft neurological signs in patients with mild and moderate Alzheimer’s disease.

Soft neurological signs	CDR 1 Mean (SD)	CDR 2 Mean (SD)	z Score	p Value
Motor coordination*	4.09 (3.86)	7.45 (4.93)	3.91	<0.001
Sensory integration*	2.88 (3.22)	5.83 (6.07)	2.66	0.008
Dyskinesia	0.03 (0.15)	0.02 (0.15)	0.38	0.70
Failure of suppression	2.96 (1.88)	4.13 (3.24)	1.24	0.22
Parkinsonism	0.07 (0.24)	0.23 (0.52)	1.73	0.08
Total*	10.06 (6.89)	17.97 (11.98)	3.24	<0.001

Abbreviations: CDR 1 = patients with mild dementia; CDR 2 = patients with moderate dementia.

* Indicates significance of difference between the 2 groups, Mann-Whitney U test.

Table 3. Correlations between scores for cognitive function and soft neurological signs in patients with Alzheimer's disease.

Cognitive function test	Soft neurological signs					Total score
	Motor coordination	Sensory integration	Dyskinesia	Suppression failure	Parkinsonism	
MMSE	-0.38*	-0.3*	-0.001	-0.15	-0.12	-0.38*
HKLLT						
Test 1	-0.23	-0.06	-0.06	-0.09	-0.06	-0.14
Test 2	-0.27	-0.07	-0.1	-0.06	-0.12	-0.19
Test 3	-0.32	-0.11	-0.07	-0.17	-0.1	-0.25
At 10 minutes	-0.04	-0.09	-0.06	-0.11	-0.06	0.12
At 30 minutes	-0.06	-0.24	-0.04	-0.12	-0.09	-0.2
Recognition	-0.33*	-0.09	-0.14	-0.13	-0.05	-0.26
Dementia rating scale						
Attention	-0.46*	-0.45*	-0.1	-0.2*	-0.21	-0.52*
Initiative/perseveration	-0.48*	-0.3	-0.11	-0.19	-0.1	-0.41*
Construction	-0.49*	-0.39*	-0.05	-0.19	-0.15	-0.52*
Conceptualisation	-0.41*	-0.25	-0.08	-0.18	-0.27	-0.41*
Memory	-0.37*	-0.19	-0.05	-0.21*	-0.19	-0.32
Total score	-0.57*	-0.39*	-0.09	-0.23*	-0.22	-0.54*
CVFT						
Total score	-0.33	-0.07	-0.2	-0.07	-0.22	-0.25

Abbreviations: MMSE = Mini-Mental State Examination; HKLLT = Hong Kong List Learning Test; CVFT = Category Verbal Fluency Test.

* Spearman correlation coefficients.

Table 4. Baseline scores for soft neurological signs in various 2-year outcome groups.

Soft neurological signs	Stable Mean (SD)	Deteriorated Mean (SD)	Deceased Mean (SD)
Motor coordination	5.01 (3.88)	6.53 (5.53)	7.20 (6.41)
Sensory integration	3.68 (2.44)	3.03 (3.29)	4.81 (5.15)
Dyskinesia	0 (0)	0.05 (0.21)	0.08 (0.26)
Failure of suppression	2.96 (1.94)	4.29 (2.89)	2.90 (1.79)
Parkinsonism*	0.07 (0.23)	0 (0)	0.50 (0.7)
Total	11.77 (7.86)	13.31 (10.82)	16.69 (12.11)

* The difference between values for the stable and deceased groups is significant, $p < 0.001$, Kruskal-Wallis and Chi squared tests.

groups. The stable group had lower scores for parkinsonian signs than the deceased group ($p = 0.003$, Mann Whitney U test). Baseline scores for failure of suppression appeared to be higher in the group who had deteriorated, but this difference did not reach significance ($p = 0.07$, Mann Whitney U test). Scores for motor coordination and sensory integration signs for the 3 outcome groups (Table 4), were not significantly different (Kruskal-Wallis test).

Discussion

Deterioration with respect to SNS serves as a clinical marker for underlying neurological deficit. SNS can be broadly classified as 'cortical' and 'subcortical' signs. Cortical signs include motor coordination and sensory integration signs and are likely to be related to degeneration or lesions of the cortical structures. Subcortical signs are mainly extrapyramidal signs such as dyskinesia and parkinsonian signs. Primitive reflexes were not found in the study population, possibly because the patients all had mild to moderate AD,

stages at which primitive reflexes would not be a common feature.

Patients with AD had significantly more sensory integration and motor coordination signs than the healthy controls. Furthermore, there was an association between the abundance of these signs and the severity of cognitive impairment. In addition, patients with moderate dementia had significantly higher ratings of these cortical SNS than those with mild dementia. It would be difficult to determine whether patients with severe dementia have an even higher number of SNS, as their impaired cognition would compromise their ability to understand test instructions. Nevertheless, for patients with dementia, the presence of SNS may indicate subtle neurological deficits reflecting underlying cortical degeneration.

The highly significant differences in SNS between participants without dementia and patients with dementia suggest that SNS assessment may be useful as a screening tool for very early AD. Further prospective studies may help to evaluate the usefulness of SNS examination as a predictive

factor for progression to clinical AD.⁶ Evaluation of the SNS profiles of patients with mild cognitive impairment would be of particular interest. Although most of these patients present with memory complaints, clinical SNS examination may provide additional information about the severity of neurological deficits.

The strong association between cortical SNS and functions in most cognitive domains suggests that these 2 symptoms represent overlapping dimensions. It is likely that both clinical assessments are influenced by and reflect underlying cortical damage. The prevalence and severity of extrapyramidal signs did not appear to be closely related to the severity of cognitive impairment. However, the very low prevalence of these subcortical signs may have compromised sensitivity for detecting possible associations with other clinical factors. However, it is possible that the presence of subcortical signs may signify additional subcortical degenerative processes of functional and prognostic significance.

The predictive value of SNS in relation to clinical progression is also of practical importance. Although SNS such as motor coordination and sensory integration were sensitive indicators of the severity of dementia and were highly correlated with cognitive function, they were not particularly predictive of clinical progression. As a sizeable proportion of patients with moderate dementia failed to show progression in terms of SNS assessment, it is possible that the window of optimum sensitivity for these signs as predictors of decline lies in the presymptomatic phase, when cortical degeneration is still at an early stage.

In the present study, it was found that baseline parkinsonian features were more prominent in patients who died prior to follow-up. As the patients recruited into this project were all naive in terms of antipsychotic medication, it is likely that extrapyramidal signs were related to underlying degeneration. The association of extrapyramidal signs with a worse prognosis and a shorter survival in patients with AD and elderly people without dementia has been documented in other studies. Gait disorder and postural reflex imbalance have been particularly associated with a faster progression towards death.⁸ The presence of extrapyramidal signs may represent additional pathology such as vascular lesions or degenerative changes with Lewy bodies. Comorbid subcortical lesions may account for a faster pace of degeneration and more significant biochemical disturbances. The tendency to develop extrapyramidal signs probably represents relative dopamine deficiency in the basal ganglia and a predisposition towards greater susceptibility to side effects and morbidity when treated with psychotropic medication. Mortality may also be related to an increased risk of vascular events, proneness to accidents, and accelerated degeneration of important subcortical structures responsible for basic physiological functions.

Although the study group was recruited from a large psychogeriatric clinic covering a population of more than 140,000 elderly people during a period of 20 months, the sample size was not large. A larger sample size would have

enabled more comprehensive analysis of the interactions between clinical deterioration and different factors without the limitations of potential type 2 errors. One of the problems with prospective studies of elderly patients with dementia has been the difficulty of standardising follow-up intervals. In the present study, the closely matched follow-up intervals between the stable and deteriorated groups helped to reduce the potential variance in cognitive performance and clinical staging arising from differences in assessment intervals. Although the information obtainable from only 1 reassessment was limited, the results highlight the significance of clinical SNS assessment for the diagnosis and management of AD. For a comprehensive evaluation of patients with mild cognitive impairment and early AD, cognitive and neurological examinations are equally important.

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