Table 1. Baseline characteristics of our patients

	CEI (n = 394)	ATI (n = 360)	LACI (n = 218)	LSCI (n = 138)	p value
Males	204 (51.8)	230 (63.9)	135 (61.9)	66 (47.8)	<0.01
Age, years (SD)	76.6 (10.3)*	71.2 (11.7)	70.9 (10.6)	71 (11.1)	<0.01[a]
Previous history of stroke	115 (29.7)	87 (24.4)	45 (20.6)	28 (20.4)	<0.05
Stroke in progress	86 (23.4)	131 (38.5)	64 (31.5)	67 (55.4)	<0.01
History of hypertension	255 (64.7)	251 (69.7)	152 (69.7)	102 (73.9)	0.18
History of diabetes mellitus	102 (26.1)	136 (37.8)	68 (31.5)	41 (29.7)	<0.01
History of dyslipidemia	119 (31.6)	149 (42.5)	98 (45.6)	60 (43.8)	<0.01
Smoking habit	67 (18.7)	118 (36.2)	74 (34.9)	26 (20.2)	<0.01
Heavy alcohol consumption	35 (9.5)	56 (17.0)	33 (15.6)	20 (15.4)	<0.05
Disturbance of consciousness	166 (42.1)	81 (22.5)	0	10 (7.2)	<0.01
Cortical dysfunction	167 (42.4)	115 (31.9)	0	6 (4.3)	<0.01
Cranial nerve finding	92 (23.4)	100 (27.8)	38 (17.4)	34 (24.6)	<0.05
Hemiparesis	298 (75.6)	268 (74.4)	184 (84.4)	124 (89.9)	<0.01
Ataxia	32 (8.1)	33 (9.2)	11 (5.0)	16 (11.6)	0.14
Sensory disturbance	50 (12.7)	66 (18.3)	64 (29.4)	27 (19.6)	<0.01
Antiplatelet drugs	138 (35.0)	291 (80.8)	190 (87.2)	121 (87.7)	<0.01
Anticoagulants	195 (49.5)	20 (5.6)	1 (0.5)	3 (2.2)	<0.01
mRS at hospitalization					<0.01
0–2	81 (21.7)	113 (33.1)	107 (54.0)	37 (31.4)	
3–5	292 (78.3)	228 (56.0)	91 (45.9)	81 (68.6)	
3	19 (5.1)	26 (7.6)	22 (11.1)	23 (19.6)	
4	20 (5.4)	41 (12.0)	42 (21.2)	22 (18.7)	
5	253 (67.8)	161 (47.2)	27 (13.6)	36 (30.6)	
mRS at discharge					<0.01
0–2 (good outcome)	138 (36.6)	160 (47.2)	142 (73.2)	62 (52.1)	
3–5 (poor outcome)	183 (48.6)	159 (46.9)	52 (26.8)	56 (47.1)	
3	48 (12.7)	58 (17.1)	33 (17.0)	35 (29.5)	
4	56 (14.9)	53 (15.6)	14 (7.2)	12 (10.2)	
5	79 (21.0)	48 (14.2)	5 (2.6)	9 (7.7)	
6 (death)	56 (14.9)	20 (5.9)	0	1 (0.8)	
Hospital stay, days (SD)	50.7 (50.0)*	51.8 (54.9)*	25.7 (28.1)*	40.1 (31.7)	<0.01[a]

Values represent numbers of patients with percentages in parentheses, except where indicated otherwise. p values were determined by χ^2 test, except where indicated otherwise. * $p < 0.05$ versus LSCI (Dunnett's post hoc test).
[a] Determined by analysis of variance.

Long-Term Prognosis of Patients with LSCI

Long-term prognosis was assessed by stroke recurrence and death. Over a 3-year period, 248 deaths were recorded. The survival curve is shown in figure 2. The mortality for each subtype was as follows: LSCI, 10 cases (8.4%); LACI, 16 cases (8.2%); ATI, 71 cases (22.3%), and CEI, 151 cases (41.1%). Hazard ratios (HRs) are shown in table 2. Stepwise multiple regression analysis identified age, gender and diabetes mellitus as independently associated with mortality. After adjusting for these factors, mortality over 3 years for LSCI was lower than that for CEIs [HR 4.26, 95% confidence interval (CI) 2.23–8.14; $p < 0.01$] or ATIs (HR 2.07, 95% CI 1.05–4.07; $p < 0.05$) and similar to that for LACIs (HR 0.72, 95% CI 0.32–1.62; $p = 0.42$). Causes of death in patients with LSCI included infection in 5 cases (pneumonia in 4, sepsis in 1), malignancy in 2 cases, renal failure in 1 case, acute posttraumatic subdural hematoma in 1 case and an unknown cause in 1 case.

Over the 3-year period, 155 stroke recurrences were observed. Recurrence-free survival is shown in figure 2. The number of recurrences for each subtype was as follows: LSCI, 11 cases (9.3%); LACI, 28 cases (14.1%); ATI, 48 cases (16.6%), and CEI, 68 cases (23.8%). Stepwise multiple regression analysis showed that age and previous history of stroke were independently associated with re-

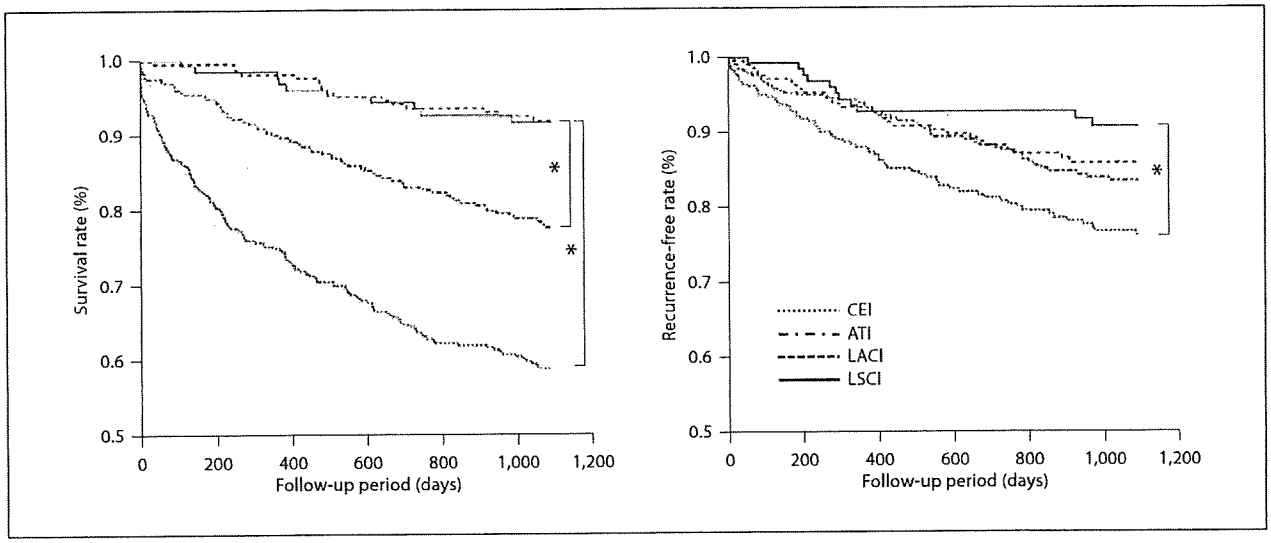

Fig. 2. Kaplan-Meier estimates of survival rates and recurrence-free rates for the 4 stroke subtypes. The survival rate of patients with LSCI showed no significant difference compared with LACIs ($p = 0.93$), but was higher than that for patients with ATIs ($p < 0.01$) and CEIs ($p < 0.01$). The survival rate for LACIs was also higher than that for ATIs ($p < 0.01$) and CEIs ($p < 0.01$). The recurrence-free rate of LSCI did not differ significantly compared to that of LACIs ($p = 0.31$) and ATIs ($p = 0.22$), but was higher than that of CEIs ($p < 0.01$). * $p < 0.01$.

Table 2. HRs and 95% CIs for death and recurrence of stroke over a 3-year follow-up period comparing LSCI with other subtypes

	CEI	ATI	LACI	LSCI
Death				
Number of patients (events)	394 (151)	360 (71)	218 (16)	138 (10)
Crude HR (95% CI)	6.15 (2.86–13.20)	2.46 (1.11–5.43)	1.05 (0.42–2.63)	1.00
p value	<0.01	<0.01	0.94	
Adjusted HR[1] (95% CI)	4.26 (2.23–8.14)	2.07 (1.05–4.07)	0.72 (0.32–1.62)	1.00
p value	<0.01	0.04	0.42	
Recurrence				
Number of patients (events)	394 (68)	360 (48)	218 (28)	138 (11)
Crude HR (95% CI)	2.80 (1.33–5.88)	1.53 (0.71–3.30)	1.51 (0.67–3.40)	1.00
p value	<0.01	0.08	0.21	
Adjusted HR[2] (95% CI)	2.59 (1.32–5.07)	1.54 (0.77–3.10)	1.48 (0.71–3.06)	1.00
p value	<0.01	0.23	0.30	

[1] Adjusted for age, gender and diabetes mellitus. [2] Adjusted for age and previous history of stroke.

currence. After adjusting for age and previous history of stroke, the recurrence rate of LSCI was lower than that of CEIs (HR 2.59, 95% CI 1.32–5.07; $p < 0.01$), but was not significantly different from that of ATIs (HR 1.54, 95% CI 0.77–3.10; $p = 0.23$) or LACIs (HR 1.48, 95% CI 0.71–3.06; $p = 0.30$). The recurrence rate of LSCI was the lowest among the 4 categories, and a significant difference was found when compared to that of CEIs (table 2). Clinical subtypes that were associated with the recurrence of LSCI included LACIs (5 cases) and IUCs (2 cases). In 4 cases, insufficient data were available for determination.

Discussion

In this study, we analyzed the long-term prognosis of patients with LSCI. We determined that the clinical characteristics of LSCI result in poor functional outcomes, similar to acute-phase ATI, and a good prognosis, similar to chronic-phase LACI. Patients suffering from LSCI display this biphasic clinical course, which is seen in 10% of all patients with ischemic stroke. Thus, LSCI may be considered to be a distinct stroke subtype.

Patients with large subcortical infarcts reportedly show cardiogenic sources in 9–52% of cases [5, 9–14] and stenosis of major arteries in 27–89.5% of cases [2, 5, 9–16]. We stress that a cardiac source or stenosis of major arteries can cause a LSCI. Therefore, a LSCI with a cardiogenic source should be classified as a CEI, and a LSCI with significant (≥50%) stenosis or occlusion of the major arteries that supply the ischemic region should be categorized as an ATI.

Our results indicate that patients with LSCI do not usually experience recurrent episodes over the long term. LSCI may be caused by atheromatous disease in the penetrating branch arteries [17]. Branch atheromatous disease completely occludes the penetrating arteries; therefore, recurrence in these arteries is not common. This mechanism may be responsible for the low recurrence rate associated with LSCI.

Our results indicate that patients with LSCI experience a severe initial attack. LSCI often involve the striatocapsular region and pyramidal tract. The clinical data revealed that approximately half of the patients showed a progressive pattern at onset (55.4%), and some of them displayed disturbances in consciousness (7.2%) or cortical dysfunction (4.3%). LSCI were associated with worse mRS than LACIs. Such a progressive pattern may be related to stroke severity.

We acknowledge that this study has several limitations. Firstly, the accuracy of subtype classification is limited. In our study, the implementation rate of TEE was low, because we performed TEE after assessing the potential risks and benefits to patients and the condition of patients in acute care hospitals. In 40–60% of cases in which TEE is performed, a cardiac source of embolism is identified [18–20]. The possibility that other stroke subtypes (ATI, LACI or IUC) were categorized as CEI in the assessment cannot be ruled out. In addition, the rate of Holter monitoring was almost as low as the rate of TEE. The Holter ECG offers a low detection rate of 2–3% for new-onset atrial fibrillation in acute stroke [21]. Therefore, the Holter monitoring rate had an insignificant effect on the diagnosis of CEI. However, despite this limitation, we were able to identify differences between the long-term prognosis for LSCI and that for CEI or ATI. In our opinion, applying our examination system in routine clinical practice could clarify the clinical characteristics of LSCI. We also evaluated lesion size using DWI or FLAIR in 88.9% of cases and CT in the remaining cases during the early stage after onset. A lesion ≥15 mm in diameter on DWI could actually be <15 mm in diameter, as the apparent size of a lesion in acute ischemic infarction appears larger on DWI due to edema. Lee et al. [22] reported that the use of DWI/MRA within 24 h of hospitalization substantially improves the accuracy of diagnosis of the early ischemic stroke subtype, and that diagnosis by DWI/MRA within 24 h is the same as the final diagnosis in 94% of cases. Our diagnosis of the stroke subtype using DWI or FLAIR was thus fairly accurate; however, a few cases of LACI may have been classified as the LSCI subtype. Secondly, patients at each facility were managed using nonstandardized treatment protocols, and their effects on survival and recurrence remain unknown. Thirdly, our investigation was limited to the assessment of survival and recurrence, and we did not assess activities of daily living during the 3-year period. Thus, future studies should also include assessment of activities of daily living.

Summary

The short-term prognosis of functional outcomes of LSCI is poor, similar to that of ATIs in the acute phase. However, mortality and recurrence rates for LSCI are low, resembling those for LACIs. This information on the prognoses of patients with LSCI should prove helpful to medical staff and patients who remain disabled due to this condition.

Acknowledgments

The authors wish to thank the many doctors, medical coworkers and investigators who participated in the Tottori University Lacunar Infarction Prognosis Study for their cooperation.

References

1 Halkes PHA, Kappelle LJ, van Gijn J, van Wijk I, Koudstaal PJ, Algra A: Large subcortical infarcts: clinical features, risk factors, and long-term prognosis compared with cortical and small deep infarcts. Stroke 2006; 37:1828–1832.

2 Horowitz DR, Tuhrim S: Stroke mechanisms and clinical presentation in LSCI. Neurology 1997;49:1538–1541.

3 Special Report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular disease. III. Stroke 1990;21:637–676.

4 Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE; the TOAST Investigators: Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. Stroke 1993;24:35–41.

5 Donnan GA, Bladin PF, Berkovic SF, Longley WA, Saling MM: The stroke syndrome of striatocapsular infarction. Brain 1991;114: 51–70.

6 Soda T, Nakayasu H, Maeda M, Kusumi M, Kowa H, Awaki E, Saito J, Nakashima K: Stroke recurrence within the first year following cerebral infarction – Tottori University Lacunar Infarction Prognosis Study. Acta Neurol Scand 2004;110:343–349.

7 Tatu L, Moulin T, Bogousslavsky J, Duvernoy H: Arterial territories of human brain: brainstem and cerebellum. Neurology 1996; 47:1125–1135.

8 Tatu L, Moulin T, Bogousslavsky J, Duvernoy H: Arterial territories of the human brain: cerebral hemispheres. Neurology 1998;50:1699–1708.

9 Weiller C, Ringelstein EB, Reiche W, Thron A, Buell U: The large striatocapsular infarct. A clinical and pathophysiological entity. Arch Neurol 1990;47:1085–1091.

10 Levine RL, Lagreze HL, Dobkin JA, Turski PA: Large subcortical hemispheric infarctions. Presentation and prognosis. Arch Neurol 1988;45:1074–1077.

11 Boiten J, Lodder J: Large striatocapsular infarcts: clinical presentation and pathogenesis in comparison with lacunar and cortical infarcts. Acta Neurol Scand 1992;86:298–303.

12 Nicolai A, Lazzarino LG, Biasutti E: Large striatocapsular infarcts: clinical features and risk factors. J Neurol 1996;243:44–50.

13 Min WK, Park KK, Kim YS, Park HC, Kim JY, Park SP, Suh CK: Atherothrombotic middle cerebral artery territory infarction: topographic diversity with common occurrence of concomitant small cortical and subcortical infarcts. Stroke 2000;31:2055–2061.

14 Bladin PF, Berkovic SF: Striatocapsular infarction: large infarcts in the lenticulostriate arterial territory. Neurology 1984;34:1423–1430.

15 Nakano S, Yokogami K, Ohta H, Goya T, Wakisaka S: CT-defined large subcortical infarcts: correlation of location with site of cerebrovascular occlusive disease. Am J Neuroradiol 1995;16:1581–1585.

16 Oiwa K, Yamamoto Y, Hayashi M, Kasai T: Mechanisms involved in large subcortical infarcts (in Japanese). Rinsho Shinkeigaku 2001;41:475–481.

17 Caplan LR: Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology 1989;39: 1246–1250.

18 de Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, Bollen EL, Bax JJ: Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. Stroke 2006;37:2531–2534.

19 Strandberg M, Marttila RJ, Helenius H, Hartiala J: Transoesophageal echocardiography in selecting patients for anticoagulation after ischaemic stroke or transient ischaemic attack. J Neurol Neurosurg Psychiatry 2002; 73:29–33.

20 Cujec B, Polasek P, Voll C, Shuaib A: Transesophageal echocardiography in the detection of potential cardiac source of embolism in stroke patients. Stroke 1991;22:727–733.

21 Schaer BA, Zellweger MJ, Cron TA, Kaiser CA, Osswald S: Value of routine Holter monitoring for the detection of paroxysmal atrial fibrillation in patients with cerebral ischemic events. Stroke 2004;35:e68–e70.

22 Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL: Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Stroke 2000;31:1081–1089.

European Journal of Neurology 2009, 16: 589–594 doi:10.1111/j.1468-1331.2009.02544.x

Assessment of dementia in patients with multiple system atrophy

M. Kitayama[a,b], K. Wada-Isoe[a], Y. Irizawa[b] and K. Nakashima[a]

[a]*Department of Neurology, Faculty of Medicine, Institute of Neurological Sciences, Tottori University, Yonago; and* [b]*Division of Legal Medicine, Department of Social Medicine, Faculty of Medicine, School of Medicine, Tottori University, Yonago, Japan*

Keywords:
cognitive impairment, Lewy body disease, MIBG cardiac scintigraphy, multiple system atrophy, α-synucleinopathy

Received 7 April 2008
Accepted 28 November 2008

Background and purpose: We investigated dementia in patients with multiple system atrophy (MSA) in order to characterize the prevalence and nature of impairments in these patients.

Methods: Fifty-eight MSA patients were recruited in our institution between April 1996 and December 2006 and investigated.

Results: Of 58 patients, 10 were diagnosed with dementia. There were no significant differences in age at onset, gender, duration of disease, or severity of cerebellar dysfunction between patients with and without dementia. The early and delayed heart to mediastinum (H/M) ratios obtained with ^{123}I-metaidobenylguanidine (MIBG) cardiac scintigraphy were significantly decreased in patients with dementia compared with those without dementia. Of the 10 patients with dementia, three were found to have cognitive decline that preceded onset of motor symptoms. White matter lesions were evident in these patients, whilst frontal atrophy was prominent in patients whose cognitive decline was preceded by onset of motor symptoms.

Conclusions: Dementia in patients with MSA may be more common than previously thought, furthermore, we speculate that clinical features of dementia in these patients might be heterogeneous.

Introduction

Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disease, characterized clinically by combinations of ataxia, pyramidal signs, parkinsonism, and autonomic dysfunction. MSA is separated into two major clinical subtypes: MSA-P (striatonigral degeneration) with predominant parkinsonian features and MSA-C (olivopontocerebellar atrophy) with predominant cerebellar ataxia. Inclusion of autonomic dysfunction, common to all forms of MSA and referred to previously as Shy-Drager syndrome, has been discouraged in the consensus criteria [1]. Neuropathology significantly affects subcortical areas; most specifically, the gray matter of the substantia nigra, striatum, inferior olivary nucleus, pontine nuclei, and cerebellum [2]. The histological hallmark is the presence of glial cytoplasmic inclusions (GCI) in oligodendroglia: Demonstration is required for a definite diagnosis [3]. Neuronal and astroglial cytoplasmic inclusions of similar composition are found in many brain areas. Recently, it was reported that the main components of these inclusions were α-synuclein, and MSA is now classified amongst the 'α-synucleinopathies' along with Parkinson's disease (PD) and dementia with Lewy bodies. Accumulation of α-synuclein in patients with MSA is also found in neuronal cell bodies and processes in several brain regions [4–7].

The frequency of cognitive impairment is 20–40% in patients with clinical MSA, although general intellectual dysfunctions such as dementia are excluded from criteria for diagnosis of MSA [1,8,9]. Reports suggest that cognitive impairment in patients with MSA involves the frontal lobe, presenting as frontal-executive dysfunction rather than impairment of memory [10–15]. However, cognitive dysfunction in these patients is not fully understood. In this research, we clinically evaluated hospitalized patients with MSA cared for by our department in order to clarify clinical features, especially those regarding dementia.

Methods

Participants

Participants were 58 patients with MSA who were admitted to the Department of Neurology, Tottori University Hospital, Japan between April 1996 and December 2006. Patients were diagnosed with possible

Correspondence: Michio Kitayama, Department of Neurology, Faculty of Medicine, Institute of Neurological Sciences, Tottori University, 36-1 Nishi-cho, Yonago, 683-8504, Japan (tel.: +81 859 38 6757; fax: +81 859 38 6759; e-mail: mickita@med.tottori-u.ac.jp).

or probable MSA according to the consensus criteria, excluding criteria of dementia because that has not been adopted into any formal criteria for MSA with dementia. Patients were examined by at least two neurologists board-certified by the Japanese Neurological Society. We used the International Cooperative Ataxia Rating Scale (ICARS) [16] and the Mini Mental State Examination (MMSE) for all patients. A complete neurological examination was also performed for all patients, including blood analysis, cerebrospinal fluid studies, and imaging of the head with magnetic resonance imaging (MRI). All MRI studies were performed on either 1.5-T or 3.0-T units. T1- and T2-weighted images and fluid attenuated inversion recovery sequences were obtained. Definitions and gradings of cerebral atrophy, especially frontal lobes were qualitatively estimated by two neurologists blind to the clinical findings. White matter hyperintensities severity ratings were attained from T2-weighted images according to the Fazekas scale [17]. Twenty-seven patients also underwent ^{123}I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy. Demographic features of patients are shown in Table 1.

Clinical diagnosis of MSA was based on consensus criteria excluding dementia [1]. Diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition-revised (DSM-IV) criteria, scored ≥1.0 on the Clinical Dementia Rating scale [18] and scored ≤24 on MMSE. All participants described in this study were approved by the Ethics Review Committee of School of Medicine, Tottori University and informed consent was obtained from each subject.

Statistical analysis

Data analysis was conducted with SPSS for Windows (version 15; SPSS Inc., Chicago, IL, USA). Results are presented as the mean ± standard deviation. Comparison of means was performed using the Mann–Whitney *U*-analysis for independent samples. Categorical variances were examined using the chi-squared test. A *P*-value <0.05 was accepted as significant. Differences in heart to mediastinum (H/M) ratios between groups were evaluated using analysis of covariance (ANCOVA) adjusted for patient age as the covariate.

Table 1 Comparison of clinical features between multiple system atrophy (MSA) patients with and without dementia

	MSA without dementia $n = 17$	MSA with dementia $n = 10$	*P*-value
Age at evaluation (year)	59.8 ± 8.1	64.3 ± 6.8	0.145
Age at onset (year)	56.2 ± 8.2	60.4 ± 6.5	0.258
Gender (M/F)	6/11	4/6	0.178[a]
Disease duration (year)	3.2 ± 2.1	3.9 ± 1.6	0.523
ICARS	41.5 ± 15.6	49.6 ± 22.6	0.419
MMSE	27.9 ± 2.3	21.3 ± 2.3	<0.001
Early H/M ratio	2.29 ± 0.26	1.78 ± 0.31	0.001
Delayed H/M ratio	2.30 ± 0.34	1.62 ± 0.46	0.003
Washout rate	27.3 ± 5.35	38.2 ± 9.70	0.018

P-value: Mann–Whitney *U*-test. [a]Chi-squared test; H/M, heart to mediastinum.

Results

Demographics of patients

Of all 58 patients, 49 (84%) were classified as MSA-C, nine patients (16%) were classified as MSA-P. Ten patients with MSA (17%) were diagnosed with dementia. All patients with dementia were clinically diagnosed as MSA-C type and have not experienced visual hallucinations.

Comparison of ^{123}I-MIBG cardiac scintigraphy between patients with and without dementia

We evaluated ^{123}I-MIBG cardiac scintigraphy in 27 patients, including 10 patients with dementia and 17 patients without dementia. Demographic features of these patients are shown in Table 1. Whilst age at onset, gender, disease duration, and severity of ataxia (ICARS) did not differ between groups, the early and delayed H/M ratio of ^{123}I-MIBG cardiac scintigraphy were significantly decreased in patients with dementia compared with those without dementia.

Clinical features of patients with dementia

The clinical features of MSA *patients with dementia* are shown in Table 2. Whilst seven patients were found to have cognitive decline preceded by ataxia, three patients had dementia develop within 1 year prior to onset of ataxia. The latter three patients were initially diagnosed as dementia with Alzheimer type (DAT).

The seven patients (cases 1–7) whose dementia occurred after onset of ataxia showed mild or moderate frontal lobe atrophy by MRI and decreased regional cerebral blood flow (rCBF) in the frontal lobe by SPECT, but none had cerebral white matter lesions by MRI. In contrast, the latter three patients (cases 8–10), whose dementia developed before onset of ataxia, had both moderate or severe cerebral atrophy and cerebral white matter lesions. Clinically, disorientation was more severe in these three patients than in the other seven patients. Clinically, memory

Table 2 Summary of multiple system atrophy patients with dementia

Case	Gender	Onset age	Disease duration	Initial symptom	ICARS	MMSE	Frontal lobe atrophy	WMH severity	H/M ratio (early/delayed)
1	F	71	2	Ataxia	32	23	+	–	1.88/1.72
2	F	52	2	Ataxia	45	24	+	–	1.73/1.43
3	F	54	3	Ataxia	33	22	+	–	2.04/2.29
4	M	53	3	Ataxia	49	21	+ +	–	1.61/1.38
5	M	62	5	Ataxia	53	20	+	–	1.82/2.09
6	F	58	6	Ataxia	90	23	+ + +	–	1.34/1.04
7	M	59	7	Ataxia	71	21	+ +	–	1.43/1.13
8	F	58	3	Dementia	23	18	+ + +	+	2.06/1.58
9	M	64	4	Dementia	94	9	+ +	+ +	1.47/1.21
10	F	69	6	Dementia	34	18	+ + +	+ + +	2.38/2.37

Gradings of frontal lobe atrophy were estimated qualitatively; +: slight, + +: moderate, + + +: severe, white matter hyperintensities (WMH) severity ratings were attained according to the Fazekas scale; –: grade 0, +: grade 1, + +: grade 2, + + +: grade 3; ICARS, International Cooperative Ataxia Rating Scale; MMSE, Mini Mental State Examination; H/M, heart to mediastinum.

impairment and disorientation in the same three patients were more severe than seen in the other seven patients.

Representative cases

Case 7

The patient was a 66-year-old man with no family history of neurological disease and no history of major illness. He presented initially with gait disturbance and orthostatic hypotension at age 59 years and was diagnosed with MSA by a neurologist. The following year, he gradually developed dysarthria, ataxia and neuropathic bladder, and his family detected cognitive impairment. At age 62 years, he was admitted to our hospital, where he presented with ataxia, extrapyramidal signs, and dysautonomia. ICARS score was 36 points and MMSE score was 24 points. At age 65 years, his ICARS score was 71 points, MMSE score was 21 points, and intelligence quotient was 71 (VIQ 83, PIQ 60) with the Wechsler adult intelligence scale-revised (WAIS-R) and 10 points in frontal assessment battery. His lowest scored category in MMSE and WAIS-R was attention, calculation, and verbal frequency. MRI study disclosed typical findings of MSA such as severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign' and moderate frontal lobe atrophy [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. ^{99}mTc-ECD SPECT image revealed moderate decline of rCBF in the frontal lobe (Fig. 1). H/M ratio in ^{123}I-MIBG cardiac scintigraphy was 1.43/1.13 (early/delayed phase). Symptoms continued to progress gradually and he became bed-ridden at age 65 years.

Case 9

The patient was a 75-year-old man with no family history of neurological disease who had a several-year history of diabetes mellitus. At age 69, he had developed episodic memory impairment and disorientation; he was diagnosed with DAT by a neurologist. At this time, mild bilateral temporal atrophy was detected by MRI, whereas no cerebellar or pontine atrophy was evident. At age 70, gait disturbance gradually developed and he was admitted to our hospital. He was diagnosed with MSA based on the presence of severe ataxia, parkinsonism, and dysautonomia. He showed severe episodic memory impairment, disorientation, and constructional apraxia. MRI revealed typical MSA findings and moderate fronto-temporal lobe atrophy. Furthermore, there were moderate leukoaraiosis in deep white matter around anterior and posterior horn of lateral ventricles. ^{99}mTc-ECD SPECT image revealed severe decline of rCBF in the frontal and temporal lobes (Fig. 2). His ICARS score was 80 points. With cognitive assessment, he was found to have an MMSE score of 15 points and WAIS-R IQ of 62 (VIQ 76, PIQ 54). His lowest scored category in MMSE and WAIS-R was not only attention, calculation, and verbal fluency, but also severe disorientation. His symptoms progressed gradually and he became bedridden at age 72 years. At that time, ICARS score was 94 points and MMSE score was 9 points. H/M ratio in ^{123}I-MIBG cardiac scintigraphy was 1.46/1.12 (early/delayed phase). His symptoms continued to progress gradually and he died suddenly at age 73 years.

Discussion

In this study, we documented dementia in a significant proportion of patients with MSA in our hospital. Dementia is included in exclusion criteria in the consensus criteria for MSA. Of our patients, 10 (17%) were diagnosed with dementia. We classified two types of MSA with dementia. One group (cases 1–7) had

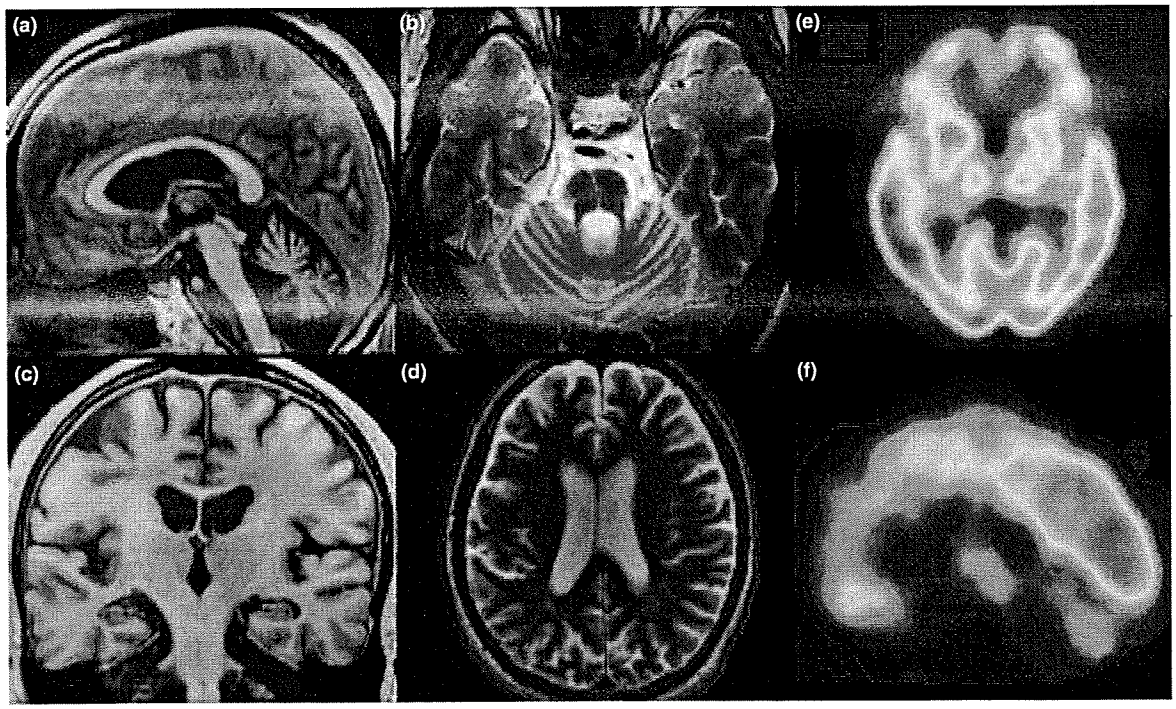

Figure 1 Neuroimaging studies at case 7. (a–d) Magnetic resonance imaging (MRI) revealed severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign,' moderate fronto-temporal lobe atrophy [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. White matter lesions were not noted. (e, f) 99mTc-ECD SPECT image showed moderate decline of regional cerebral blood flow in the frontal and temporal lobes. (a, c) T1 weighted MRI image. (b, d) T2 weighted MRI image.

dementia that was preceded by development of ataxia. The other three patients (cases 8–10) developed dementia before onset of ataxia. The common characteristics of cognitive impairment in each type of MSA with dementia included frontal executive dysfunction, findings similar to those of previous studies [10–15]. The latter type of dementia (cases 8–10) was diagnosed as DAT before criteria were reached for MSA. According to qualitative analyses of MRI, these patients showed more severe disorientation and more severe cerebral atrophy, with cerebral white matter lesions more prominent than in the other type of patient.

Moreover, we found that the patients with MSA and dementia had significantly reduced ^{123}I-MIBG cardiac uptake compared with the patients without dementia. Recent studies have reported that H/M ratio of ^{123}I-MIBG cardiac scintigraphy is a useful diagnostic tool for LBDs based on evidence of post-ganglionic cardiac sympathetic denervation in these patients [19–22]. Although MSA is also an α-synucleinopathy, H/M ratio of ^{123}I-MIBG cardiac scintigraphy in patients with MSA has been reported predominantly to be in the normal range. These published results support the hypothesis that post-ganglionic cardiac sympathetic denervation might be evident in MSA patients with dementia. However, it has not yet been clarified whether decreased cardiac uptake of MIBG is associated with neuropathological changes of the central nervous system and neuropsychological state. We have found that reduction of cardiac MIBG uptake might be associated with neuropsychological state in patients with PD [23]. Nagayama *et al.* [24] has reported a MSA case with reduction of MIBG uptake and Lewy body pathology. However, it has not been described whether the MSA case had dementia. In our study, whilst there was no neuropathological examination, we could not diagnose any type of dementia in these cases neuropathologically.

Recent studies reported that there are neuropathological changes in patients with MSA and dementia [25–27]. These reports described autopsy cases with remarkable frontal lobe atrophy, in which GCI were abundant in the deep layer of the cortex and were even more abundant in the white matter of the frontal and parietal lobes. Piao *et al.* [28] emphasized that α-synuclein and phosphorylated tau co-occurred in certain brain regions in two cases of combined MSA and AD. Moreover, only a few reports have described the

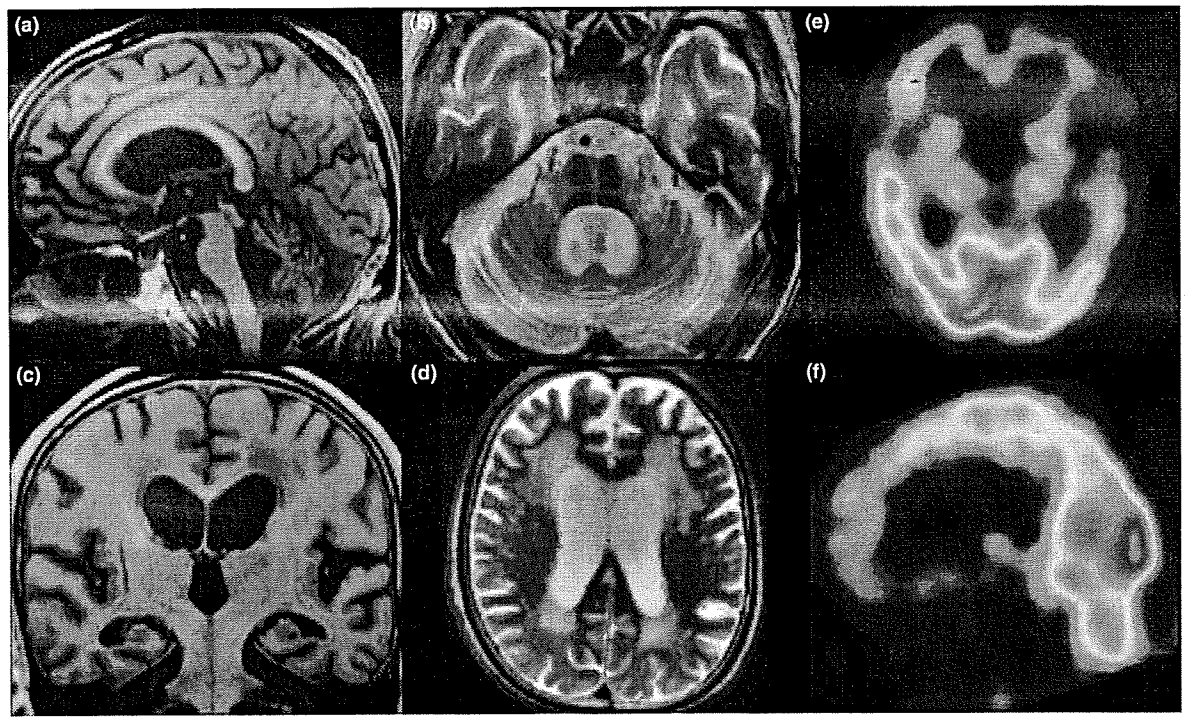

Figure 2 Neuroimaging studies at case 9. (a–d) Magnetic resonance imaging (MRI) revealed severe cerebellar and pontine atrophy with the so-called 'hot cross bun sign,' severe fronto-temporal lobe atrophy and moderate white matter lesions [Correction added after online publication 31 March 2009: in the preceding sentence, 'burn' was corrected to 'bun']. (e, f) 99mTc-ECD SPECT image showed severe decline of regional cerebral blood flow in the frontal and temporal lobes. (a, c) T1 weighted MRI image (b, d) T2 weighted MRI image.

co-existence of GCIs and Lewy bodies [29,30]. Neuropathological findings associated with dementia in patients with MSA are thought to be varied. As far as we know, patients with MSA whose dementia preceded motor dysfunction have not been described to date. As autopsy was not performed in any of the cases, we could not clarify the neuropathological correlates of dementia in our series. Therefore, neuropathological examination is necessary to clarify a new subtype of MSA. Thus, further study including postmortem neuropathological examination is needed.

In conclusion, dementia in patients with MSA may be more common than previously thought. Etiology of cognitive decline in these patients may be varied, with heterogeneous underlying pathogenetic processes.

Acknowledgements

We would like to thank the staff of the Department of Neurology, Tottori University, for their help in recruiting patients. This work was supported in part by grants for Surveys and Research on Specific Diseases and Ataxias and Neurodegenerative Diseases from the Ministry of Health, Labor, and Welfare of Japan.

References

1. Gilman S, Low PA, Quinn N, *et al.* Consensus statement on the diagnosis of multiple system atrophy. *Journal of the Neurological Sciences* 1999; **163:** 94–98.
2. Ozawa T, Paviour D, Quinn NP, *et al.* The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. *Brain* 2004; **127:** 2657–2671.
3. Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). *Journal of the Neurological Sciences* 1989; **94:** 79–100.
4. Papp MI, Lantos PL. The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. *Brain* 1994; **117:** 235–243.
5. Jellinger KA. Neuropathological spectrum of synucleinopathies. *Movement Disorders* 2003; **18**(Suppl. 6): S2–S12.
6. Wenning GK, Jellinger KA. The role of alpha-synuclein in the pathogenesis of multiple system atrophy. *Acta Neuropathologica* 2005; **109:** 129–140.
7. Wakabayashi K, Takahashi H. Cellular pathology in multiple system atrophy. *Neuropathology* 2006; **26:** 338–345.

8. Gilman S, May SJ, Shults CW, *et al.* The North American Multiple System Atrophy Study Group. *Journal of Neural Transmission* 2005; **112:** 1687–1694.
9. Wenning GK, Tison F, Ben Shlomo Y, *et al.* Multiple system atrophy: a review of 203 pathologically proven cases. *Movement Disorders* 1997; **12:** 133–147.
10. Robbins TW, James M, Lange KW, *et al.* Cognitive performance in multiple system atrophy. *Brain* 1992; **115:** 271–291.
11. Robbins TW, James M, Owen AM, *et al.* Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *Journal of Neurology, Neurosurgery and Psychiatry* 1994; **57:** 79–88.
12. Pillon B, Gouider-Khouja N, Deweer B, *et al.* Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58:** 174–179.
13. Meco G, Gasparini M, Doricchi F. Attentional functions in multiple system atrophy and Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1996; **60:** 393–398.
14. Bak TH, Crawford LM, Hearn VC, *et al.* Subcortical dementia revisited: similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). *Neurocase* 2005; **11:** 268–273.
15. Paviour DC, Winterburn D, Simmonds S, *et al.* Can the frontal assessment battery (FAB) differentiate bradykinetic rigid syndromes? Relation of the FAB to formal neuropsychological testing *Neurocase* 2005; **11:** 274–282.
16. Trouillas P, Takayanagi T, Hallett M, *et al.* International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. *Journal of the Neurological Sciences* 1997; **12:** 145.
17. Fazekas F, Chawluk JB, Alavi A, *et al.* MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *American Journal of Roentgenology* 1987; **149:** 351–356.
18. Hughes CP, Berg L, Danziger WL, *et al.* A new clinical scale for the staging of dementia. *The British Journal of Psychiatry* 1982; **140:** 566–572.
19. Orimo S, Ozawa E, Nakade S, *et al.* (123)I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1999; **67:** 189–194.
20. Yoshita M, Taki J, Yokoyama K, *et al.* Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. *Neurology* 2006; **66:** 1850–1854.
21. Orimo S, Amino T, Takahashi A, *et al.* Cardiac sympathetic denervation in Lewy body disease. *Parkinsonism and Related Disorders* 2006; **12**(Suppl. 2): S99–S105.
22. Nagayama H, Hamamoto M, Ueda M, *et al.* Reliability of MIBG myocardial scintigraphy in the diagnosis of Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76:** 249–251.
23. Kitayama M, Wada-Isoe K, Irizawa Y, Nakashima K. Association of visual hallucinations with reduction of MIBG cardiac uptake in Parkinson's disease. *Journal of the Neurological Sciences* 2008; **264:** 22–26.
24. Nagayama H, Yamazaki M, Ueda M, *et al.* Low myocardial MIBG uptake in multiple system atrophy with incidental Lewy body pathology: an autopsy case report. *Movement Disorders* 2008; **15:** 1055–1057.
25. Konagaya M, Sakai M, Matsuoka Y, Konagaya Y, Hashizume Y. Multiple system atrophy with remarkable frontal lobe atrophy. *Acta Neuropathologica* 1999; **97:** 423–428.
26. Wakabayashi K, Ikeuchi T, Ishikawa A, Takahashi H. Multiple system atrophy with severe involvement of the motor cortical areas and cerebral white matter. *Journal of the Neurological Sciences* 1998; **156:** 114–117.
27. Shibuya K, Nagatomo H, Iwabuchi K, *et al.* Asymmetrical temporal lobe atrophy with massive neuronal inclusions in multiple system atrophy. *Journal of the Neurological Sciences* 2000; **179:** 50–58.
28. Piao YS, Hayashi S, Hasegawa M, *et al.* Co-localization of alpha-synuclein and phosphorylated tau in neuronal and glial cytoplasmic inclusions in a patient with multiple system atrophy of long duration. *Acta Neuropathologica* 2001; **101:** 285–293.
29. Mochizuki A, Komatsuzaki Y, Shoji S. Association of Lewy bodies and glial cytoplasmic inclusions in the brain of Parkinson's disease. *Acta Neuropathologica* 2002; **104:** 534–537.
30. Sikorska B, Papierz W, Preusser M, Liberski PP, Budka H. Synucleinopathy with features of both multiple system atrophy and dementia with Lewy bodies. *Neuropathology and Applied Neurobiology* 2007; **33:** 126–129.

Original Paper

Neuro epidemiology

Neuroepidemiology 2009;32:263–269
DOI: 10.1159/000201565

Received: July 14, 2008
Accepted: December 8, 2008
Published online: February 11, 2009

Changes in Prevalence and Incidence of Parkinson's Disease in Japan during a Quarter of a Century

Mika Yamawaki Masayoshi Kusumi Hisanori Kowa Kenji Nakashima

Department of Neurology, Institute of Neurological Sciences, Faculty of Medicine, Tottori University, Yonago, Japan

Key Words
Parkinson's disease · Epidemiology · Japan

Abstract
Background/Aim: To determine the prevalence and incidence of Parkinson's disease (PD) and compare them with results from our previous studies. ***Methods:*** We examined epidemiological characteristics of PD patients using a service-based study in Yonago City, and a door-to-door study in Daisen Town. The prevalence days were April 1, 2004 in Yonago, and April 1, 2003 in Daisen. ***Results:*** In Yonago, we identified 254 PD patients. The crude prevalence was 180.3 (95% CI, 158.1–202.4) per 100,000 population. The adjusted prevalence was 145.8 (95% CI, 145.2–146.5) in 1980, 147.0 (95% CI, 146.3–147.6) in 1992, and 166.8 (95% CI, 166.1–167.5) in 2004, when calculated using the Japanese population in 2004. The crude incidence was 18.4 (95% CI, 11.3–25.5) per 100,000 population per year. The crude incidence in 1980 was 10.2 (95% CI, 4.6–15.8), and the adjusted incidence was 9.8 (95% CI, 4.3–15.3) in 1992, and 10.3 (95% CI, 4.7–15.9) in 2004, when calculated using the population in Yonago in 1980. In Daisen, there were 21 PD patients. The crude prevalence was 306.6 (95% CI, 175.7–437.6) and the adjusted prevalence was 192.6 (95% CI, 191.9–193.8). ***Conclusions:*** The prevalence of PD had increased, primarily because the population had aged. Differences in prevalence between these adjacent areas may have resulted from differences in the methods of investigation.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. In 1980 and 1992, we performed epidemiological studies of PD in Yonago City in Japan [1, 2], but there have been few long-term studies of this kind in the same areas. In addition, the prevalence of PD as determined by door-to-door studies may be greater than by other approaches such as service-based studies [3]. We therefore wanted to extend our previous studies longitudinally, using the same methods and diagnostic criteria to determine the prevalence and incidence of PD. Since PD has an insidious onset and slow progression, a clinical diagnosis is especially difficult in the early stages of the disease. We therefore performed the investigation twice. We also attempted to determine why patients diagnosed in the second investigation had escaped notice during the first investigation. Furthermore, we intended

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0251–5350/09/0324–0263$26.00/0

Accessible online at:
www.karger.com/ned

Mika Yamawaki, MD
Department of Neurology
Institute of Neurological Sciences Faculty of Medicine, Tottori University
36-1 Nishi-cho, Yonago 683-8504 (Japan)
Tel. +81 859 38 6757, Fax +81 859 38 6759, E-Mail mika.y@med.tottori-u.ac.jp

Table 1. Population and number of patients in Yonago and Daisen

Age	Yonago								
	men			women			total		
	population	cases	prevalence	population	cases	prevalence	population	cases	prevalence
0–39	32,412	–	–	32,128	–	–	64,540	–	–
40–44	4,022	1	24.9	4,262	1	23.5	8,284	2	24.1
45–49	4,332	–	–	4,365	–	–	8,697	–	–
50–54	4,936	2	40.5	5,187	4	77.1	10,123	6	59.3
55–59	5,212	3	57.6	5,477	4	73.0	10,689	7	65.5
60–64	4,296	8	186.2	4,742	14	295.2	9,038	22	243.4
65–69	3,584	7	195.3	4,186	16	382.2	7,770	23	296.0
70–74	3,219	17	528.1	4,072	24	589.4	7,291	41	562.3
75–79	2,530	27	1,067.2	3,835	53	1,382.0	6,365	80	1,256.9
80–84	1,346	12	891.5	2,811	28	996.1	4,157	40	962.2
85–89	586	6	1,023.9	1,559	15	962.2	2,145	21	979.0
90+	310	3	967.7	1,067	9	843.5	1,377	12	871.5
Age unknown	279			156			435		
	67,064	86	128.2	73,847	168	227.5	140,911	254	180.3

Prevalence was defined as the number of PD patients per 100,000 population. – = There were no cases for the age and sex groups.

to compare the results to those from our studies in the neighboring area, Daisen Town, in which we used different methods of investigation. We also used data collected door-to-door to determine the prevalence of PD, and we analyzed differences in results obtained with the different methods of the PD survey.

Methods

Service-Based Study in Yonago

We conducted a service-based study of PD in Yonago, a city in western Japan. During 1980, and from 1992 through 2004, the population increased, from 126,097 at the end of 1980, to 132,315 in 1992, and to 140,911 in 2004. Concurrently, the proportion of those over 65 years of age increased from 10.3% at the end of 1980 to 13.9% in 1992, and 20.7% in 2004. Since 1980, the migration rate had been stable, ranging from 9.2 to 11.0%. There were 12 general hospitals, 118 clinics, 8 geriatric health service facilities, and in addition, the University Hospital to serve as a neurological center. From January to October 2005, and from August 2006 to September 2007, we examined PD patients using the same method as in our previous studies [1, 2]. We recorded the patients' age, age at onset, duration and severity of disease, and complications.

Door-to-Door Study in Daisen

Daisen is located near Yonago. During the previous 12 years, the population decreased from 7,685 in 1991 to 6,849 in 2003, and the proportion of those over 65 years of age increased from 21.5 to 28.0%. We sent questionnaires to all inhabitants over 20 years of age to screen for those who showed symptoms suggestive of parkinsonism. We also conducted searches of patient documentation, including population stroke screening records, records for long-term care insurance, records of bedridden patients, and intractable disease surveys performed by community health nurses. Volunteer health officers in each small community were also interviewed to determine whether they knew of any individuals with parkinsonism in their communities. To confirm the diagnosis of PD, neurologists met with the candidates and their family members, at home or in official daycare centers.

Data Analysis

Diagnoses of PD were based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [4]. Disease severity was described according to the Hoehn and Yahr (H&Y) scale score [5]. Prevalence was defined as the number of PD patients per 100,000 people living in Yonago on April 1, 2004, and in Daisen on April 1, 2003. The crude incidence of PD was defined as the number of new PD cases per 100,000 per year, and was determined as the average for the period from 2000 to 2004 in Yonago. To determine the age- and sex-adjusted prevalence, we used the Japanese population in 2004, and for the age- and sex-adjusted incidence, we used the population of Yonago in 1980.

The mean values for the two groups were analyzed using the Mann-Whitney U test. The mean values for three groups were analyzed using the one-way analysis of variance with a post hoc comparison: Tukey-Kramer test. The difference of the prevalence was evaluated using Fisher's exact test for 10-year intervals up to over 80 years of age. Differences in severity were analyzed using

Daisen									Japan in 2004 (thousand persons)		
men			women			total			men	women	total
population	cases	prevalence	population	cases	prevalence	population	cases	prevalence	population	population	population
1,316	–	–	1,245	–	–	2,561	–	–	30,289	29,166	59,455
187	–	–	183	–	–	370	–	–	3,976	3,933	7,909
228	–	–	219	–	–	447	–	–	3,936	3,918	7,854
311	–	–	306	–	–	617	–	–	4,633	4,667	9,300
279	–	–	245	–	–	524	–	–	4,762	4,878	9,640
211	–	–	202	–	–	413	–	–	4,193	4,459	8,652
192	–	–	250	1	400.0	442	1	226.2	3,484	3,859	7,344
212	3	1,415.1	258	3	1,162.8	470	6	1,276.6	2,951	3,515	6,465
176	2	1,136.4	272	2	735.3	448	4	892.9	2,168	2,930	5,098
88	–	–	206	4	1,941.8	294	4	1,360.5	1,130	2,105	3,235
49	1	2,040.8	123	4	3,252.0	172	5	2,907.0	526	1,193	1,718
23	–	–	68	1	1,470.6	91	1	1,098.9	247	769	1,016
3,272	6	183.4	3,577	15	419.4	6,849	21	306.6	62,295	65,392	127,687

Table 2. Comparison of the two investigations

	Yonago			Daisen
	1st investigation	2nd investigation	total	
Patients	220	34	254	21
Age, years	75.3 ± 9.6	72.9 ± 7.3	75.0 ± 9.3	79.0 ± 7.0
Age at onset, years	68.6 ± 10.7	68.9 ± 7.4	68.7 ± 10.3	72.2 ± 7.7
Duration of illness, years	6.5 ± 5.4	3.4 ± 4.1[1]	6.1 ± 5.3	6.7 ± 6.0
H&Y scale score	3.3 ± 1.0	2.9 ± 1.0[1]	3.3 ± 1.0	3.8 ± 0.9[2]

[1] Significant difference relative to the 1st investigation.
[2] Significant difference relative to results in Yonago (total).

Fisher's exact test. $p < 0.05$ was considered statistically significant. We used the Statistical Package for the Social Sciences v. 15.0 (SPSS, Chicago, Ill., USA).

These studies were approved by the Ethical Review Board of the Tottori University Faculty of Medicine.

Results

Service-Based Study in Yonago

One hundred and seven (77.0%) medical institutions responded in the first investigation and 136 (97.8%) medical institutions responded in the second investigation, which provided us with 254 patients with PD (table 1). Of the 241 patients in the first investigation diagnosed with PD, 21 patients (8.7%) became ineligible in the second investigation by the clinical diagnostic criteria. Thirty-four of the 254 patients (13.4%) were newly diagnosed in the second investigation. The H&Y scale score and mean duration of illness were significantly lower in the second investigation (table 2), and the patients had generally received diagnoses of different disorders at the first investigation or had shown milder motor deterioration and mild symptoms (table 3). Table 2 summarizes the characteristics of the PD patients. There were no significant

Table 3. Summary of the 2nd investigation

	Cases
Different diagnosis at the 1st investigation	15
Essential tremor	2
Other movement disabilities[1]	7
Parkinson syndrome[2]	6
Predominant tremor with little motor deterioration	7
Extremely early stage at the 1st investigation	6
Previously diagnosed[3]	2
Accidental[4]	2
Limited follow-up information	2
Total	34

[1] Such as paralysis by cerebral infarction, osteoarthritis, spinal canal stenosis, and thyropathy.

[2] Including vascular, progressive supranuclear palsy, and drug-induced.

[3] They did not have continual checkups at a medical institution because their motor disorders were mild.

[4] They were incidentally diagnosed after hospitalization for a thigh bone or collum femoris fracture.

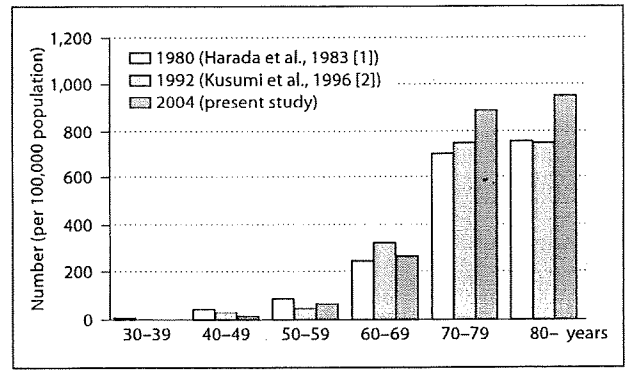

Fig. 1. Comparison of age-specific prevalence of PD. The crude prevalence tended to decrease in those less than 50 years of age, and to increase in those greater than 70 years of age.

gender differences in the patients' mean age (men, 74.1 ± 9.3 years; women, 75.5 ± 9.3 years), mean age at onset (men, 68.0 ± 10.4 years; women, 69.0 ± 10.3 years), duration of illness (data not shown) or H&Y scale score (men, 3.3 ± 1.1; women, 3.3 ± 0.9). There were 3.6% (men, 4.6%; women, 3.0%) of patients with an H&Y scale score of stage I, 15.5% (men, 19.8%; women, 13.3%) in stage II, 41.4% (men, 36.0%; women, 44.3%) in stage III, 27.5% (men, 23.3%; women, 29.7%) in stage IV, and 12.0% (men, 16.3%; women, 9.7%) in stage V. The men and women did not differ significantly in rates of progression. The patients' mean age and the mean age at onset determined in 2004 were significantly increased compared with the values for 1980 and 1992 [1, 2]. There was no significant difference in duration of illness in 2004 as compared with 1992.

The crude prevalence was 180.3 (95% CI, 158.1–202.4), with 128.2 for men (95% CI, 101.2–155.3) and 227.5 for women (95% CI, 193.1–261.9), in 2004. The prevalence for those over 65 years of age was 745.6 (95% CI, 646.8–844.4). There were significant gender differences among patients 50–79 years of age. Figure 1 shows the shifting of the crude prevalence over the three studies. The prevalence for patients over 80 years of age was significantly higher in 2004 than in 1980 and 1992. The age- and sex-adjusted prevalence was 166.8 (95% CI, 166.1–167.5) in 2004. In 1992, the crude prevalence was 117.9 (95% CI, 99.4–136.4), and the age- and sex-adjusted prevalence was 147.0 (95% CI, 146.3–147.6). In 1980, the crude prevalence was 80.6 (95% CI, 64.9–96.3), and the age- and sex-adjusted prevalence was 145.8 (95% CI, 145.2–146.5). Thus, the crude prevalence in 2004 increased when compared with those in 1980 and 1992. Furthermore, the age- and sex-adjusted prevalence in 2004 was also significantly increased (fig. 2a).

In 2004, the crude incidence was 18.4 (95% CI, 11.3–25.5) with 13.8 for men (95% CI, 4.9–22.7) and 22.6 for women (95% CI, 11.8–33.5), and the age- and sex-adjusted incidence was 10.3 (95% CI, 4.7–15.9). In 1992, the crude incidence was 15.0 (95% CI, 8.4–21.6), and the age- and sex-adjusted incidence was 9.8 (95% CI, 4.3–15.3). In 1980, the crude incidence was 10.2 (95% CI, 4.6–15.8) (fig. 2b). The crude incidence increased in 2004, although the age- and sex-adjusted incidence did not change.

Door-to-Door Study in Daisen

Of the 5,828 eligible subjects in the door-to-door study performed in Daisen, 4,765 (81.8%) completed the questionnaire, and 21 patients with PD were found (tables 1, 2). Two patients (9.5%) refused medical treatment, because visiting the hospital would have been difficult as a result of advanced age. There were no significant gender differences in mean age (men, 76.0 ± 5.7; women, 80.1 ± 7.4), mean age at onset (men, 70.1 ± 5.3; women, 72.7 ± 8.7), duration of illness, or H&Y scale score (date not shown).

In 2003, the crude prevalence was 306.6 (95%CI, 175.7–437.6), with 183.4 for men (95% CI, 36.8–330.0) and 419.4

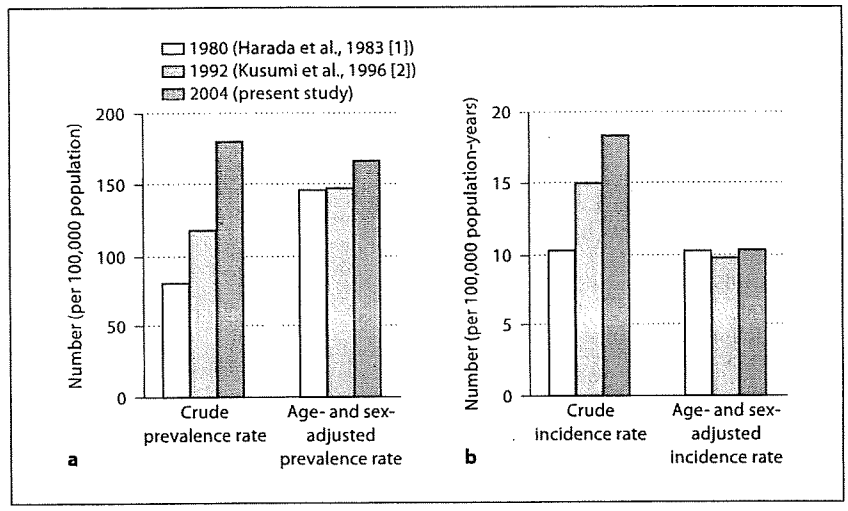

Fig. 2. Comparison of prevalence and incidence of PD. **a** The age- and sex-adjusted prevalence was significantly increased (adjusted to the Japanese population in 2004). **b** The age- and sex-adjusted incidence was not changed (adjusted to the population of Yonago in 1980).

for women (95% CI, 207.6–631.1). The prevalence for those over 65 years of age was 1,095.5 (95% CI, 629.5–1,561.4). The age- and sex-adjusted prevalence was 192.6 (95% CI, 191.9–193.8).

Discussion

This is the first study to investigate changes in the prevalence and incidence of PD in a specific area of Japan over the course of 25 years. In Yonago, we found a higher crude prevalence and incidence in this study than in our previous studies [1, 2]. One factor that contributed to the increase in crude prevalence was the aging of the population, which has been shown to be significant throughout Japan, and is reflected in the data for Yonago [6]. Others have also reported a higher prevalence of PD in the elderly [7–12]. In this study, the overall numbers and prevalence estimates of PD increased with age, confirming a role for the demographic shift. The age- and sex-adjusted prevalence was also significantly increased compared with our previous studies [1, 2]. Although the migration rate may affect prevalence figures, it had not changed during one quarter of a century in Yonago. Consequently, several other factors should be considered in our study. First, the crude prevalence was increased in elderly patients, which may indicate increasing willingness among them to consult physicians for symptoms that were previously regarded as a normal part of aging. Second, the opportunity for patients to be examined by a neurologist may have increased. The number of neurological specialists certified by the Japanese Society of Neurology grew from 14 in 1992 to 27 in 2004, and the increased awareness of PD among personal physicians, through participation in our studies, may have caused them to refer patients with parkinsonism more swiftly. Third, long-term care insurance was introduced in Japan in 2000, and elderly patients were required to undergo checkups at medical institutions in order to qualify. The environmental risk factors related to PD, including exposure to pesticides and herbicides, were reported [13–15]. In Yonago, the population that works in agriculture had decreased but whether the proportion of that population exposed to pesticides and herbicides had also decreased is not known. The contribution of these environmental factors to the observed increases in prevalence remains inconclusive. The age- and sex-adjusted prevalence may have increased as the number of consultations increased.

We found a consistently higher prevalence of PD in women than in men across almost all age groups, which is consistent with other reports in Japan [1, 2, 16, 17]. Haaxma et al. [18] reported that women with PD have a more benign phenotype, and that symptoms may develop more slowly in women because of higher striate dopamine levels, possibly related to estrogen activity. The women preponderance of PD in Japan may therefore reflect a slower rate of progression than in men. Although a significant gender difference in severity did not appear at any point in our study, we did report the slow progression of PD for women in the same area [19]. Differences in the men:women ratio between Japan and Europe may represent genetic and environmental factors that modify the risk.

Of the 254 patients with PD identified in the second investigation, 34 (13.4%) were not diagnosed during the first investigation in Yonago. The H&Y scale score and mean duration of illness were significantly lower in the second investigation than in the first. We found many mild cases, and we could calculate the higher prevalence by performing the investigation twice. Two of the 34 patients were only diagnosed after sustaining a fracture, although their fractures might have been prevented, had the diagnosis been made earlier and adequate treatment and management been provided. Patients with apparent motor dysfunction should therefore receive detailed neurological examinations to detect PD, if present, in the early stages.

When we compared the results of the two areas over the same period, we found that the age- and sex-adjusted prevalence of PD in Daisen (192.6), in comparison with Yonago (166.8), was increased by 13.4% (25.8/192.6). In principle, variations in prevalence of PD may represent differences in environmental, geographic, and genetic factors, as well as diagnostic criteria, recognition of PD, and methods used in studies [3, 7, 20]. In our studies, the diagnostic criteria and recognition of PD were consistent, hence the observed difference in prevalence was more likely related to method. Service-based studies may not include patients who have not sought medical attention, and may thereby underestimate the prevalence of PD. As reported by the Europarkinson group, this underestimation may vary from 11 to 52% [21]. The difference in prevalence might also reflect a difference in population dynamics. Daisen had an aging and decreasing population. In contrast, Yonago similarly had an aging, but increasing population. Since Yonago is an urban area and Daisen is rural, environmental factors such as exposure to pesticides and herbicides might also have had an effect [13–15]. Although we described slight differences between these two areas, they are closely adjacent and show very similar environmental profiles. In Daisen, 9.5% of patients refused medical treatment, and the service-based study did not reveal this number, even in an area of present-day Japan with raised awareness of PD. This percentage may change as inhabitants gain broader access to medical education. Eighteen percent of inhabitants in Daisen did not respond to the questionnaire, which may have further obscured the true prevalence of PD.

Conclusion

We found both higher prevalence and incidence of PD in this study than in our previous studies. Our results suggest that these increases in prevalence and incidence of PD may primarily reflect the aging of the study population and increasing opportunities for diagnosis. Early detection of PD will lead to a better quality of life for patients with this disease through earlier intervention and education.

Acknowledgement

The authors would like to thank the doctors in Yonago, and the Department of Neurology, Institute of Neurological Sciences, Faculty of Medicine, Tottori University for their cooperation. They would also like to thank the Daisen health officers. This work was supported in part by the Research Committee of CNS Degenerative Diseases, Ministry of Health, Labour and Welfare of Japan.

References

1 Harada H, Nishikawa S, Takahashi K: Epidemiology of Parkinson's disease in a Japanese city. Arch Neurol 1983;40:151–154.

2 Kusumi M, Nakashima K, Harada H, Nakayama H, Takahashi K: Epidemiology of Parkinson's disease in Yonago City, Japan: comparison with a study carried out 12 years ago. Neuroepidemiology 1996;15:201–207.

3 von Campenhausen S, Bornschein B, Wick R, Bötzel K, Sampaio C, Poewe W, Oertel W, Siebert U, Berger K, Dodel R: Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 2005;15:473–490.

4 Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.

5 Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. Neurology 1967; 17:427–442.

6 Anderson GF, Hussey P: Population aging: a comparison among industrialized countries. Health Aff 2000;19:191–203.

7 Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, Zhou B, Geng ZP, Wu JX, Wen HB, Zhao H, Zahner GE: Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet 2005;365:595–597.

8 Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, Chen ZY, Liou HH: Prevalence, incidence, and mortality of PD: A door-to-door survey in Ilan county, Taiwan. Neurology 2001;57:1679–1686.

9 de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C, Hofman A: Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurology 2000; 54(suppl 5):S21–S23.

10 Chan DK, Cordato D, Karr M, Ong B, Lei H, Liu J, Hung WT: Prevalence of Parkinson's disease in Sydney. Acta Neurol Scand 2005; 111:7–11.

11 de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meché FG, Hofman A: Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995;45:2143–2146.
12 Schrag A, Ben-Shlomo Y, Quinn NP: Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. BMJ 2000;321:21–22.
13 de Lau LM, Breteler MM: Epidemiology of Parkinson's disease. Lancet Neurol 2006;5:525–535.
14 Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S: A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology 2000;21:435–440.
15 Gorell JM, Peterson EL, Rybicki BA, Johnson CC: Multiple risk factors for Parkinson's disease. J Neurol Sci 2004;217:169–174.
16 Morriwaka F, Tashiro K, Itoh K, Honma S, Okumura H, Kikuchi S, Hamada T, Kaneko S, Kurowaka Y: Prevalence of Parkinson's disease in Hokkaido, the northernmost island of Japan. Intern Med 1996;35:276–279.
17 Kimura H, Kurimura M, Wada M, Kawanami T, Kurita K, Suzuki Y Katagiri T, Daimon M, Kayama T, Kato T: Female preponderance of Parkinson's disease in Japan. Neuroepidemiology 2002;21:292–296.
18 Haaxma CA, Bloem BR, Borm GF, Oyen WJ, Leenders KL, Eshuis S, Booij J, Dluzen DE, Horstink M: Gender differences in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:819–824.
19 Nakashima K, Maeda M, Tabata M, Adachi Y, Kusumi M, Ohshiro H: Prognosis of Parkinson's disease in Japan. Tottori University Parkinson's Disease Epidemiology (TUPDE) Study Group. Eur Neurol 1997;38(suppl 2):60–63.
20 Tan LC, Venketasubramanian N, Hong CY, Sahadevan S, Chin JJ, Krishnamoorthy ES, Tan AK, Saw SM: Prevalence of Parkinson disease in Singapore: Chinese vs Malays vs Indians. Neurology 2004;62:1999–2004.
21 de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, Alpérovitch A, Rocca WA: Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62:10–15.

Original Paper

Neuro epidemiology

Neuroepidemiology 2009;32:101–106
DOI: 10.1159/000177035

Received: June 21, 2008
Accepted: September 11, 2008
Published online: November 27, 2008

Prevalence of Dementia in the Rural Island Town of Ama-cho, Japan

Kenji Wada-Isoe[a] Yusuke Uemura[a] Yutaka Suto[a] Koji Doi[a] Keiko Imamura[a] Ai Hayashi[a] Michio Kitayama[a] Yasuhiro Watanabe[a] Yoshiki Adachi[a, b] Kenji Nakashima[a]

[a]Department of Neurology, Institute of Neurological Science, Faculty of Medicine, Tottori University, Yonago, and [b]Department of Neurology, Matsue National Hospital, Matsue, Japan

Key Words
Alzheimer's disease · Vascular dementia · Dementia with Lewy bodies · Parkinson's disease · Progressive supranuclear palsy · Frontotemporal lobar degeneration

Abstract
Background: With the striking increase in the number of elderly people in Japan, dementia has not only become a medical but also a social issue. ***Methods:*** We studied the prevalence of dementing disorders in a rural island town of Japan (Ama-cho), using a door-to-door 2-phase design. ***Results:*** Of the 120 persons screened as having cognitive impairment, 104 people were diagnosed as having dementia. The prevalence (cases/100 persons aged 65 years and older) was 11.0 for all types of dementia, 7.0 for Alzheimer's disease, 1.7 for vascular dementia, 0.53 for dementia with Lewy bodies, 0.74 for Parkinson's disease dementia, 0.21 for progressive supranuclear palsy, 0.11 for frontotemporal lobar degeneration and 0.74 for other dementia. The overall prevalence was higher in women for Alzheimer's disease and Parkinson's disease dementia, and in men, for vascular dementia and dementia with Lewy bodies. ***Conclusion:*** We confirmed the overall prevalence of dementia in the elderly population aged 65 years and older to be 11.0. This finding is higher compared with previous reports in Japan.

Introduction

Examination of the prevalence of dementia is important for health policy planning, especially in developed countries, where the increase in the number of elderly people is striking. In the past, diagnostic criteria and classification methods were not well established. Previously, many epidemiological studies in Japan have focused on only two major dementia subtypes: Alzheimer's disease (AD) and vascular dementia (VD) [1–5]. We investigated the prevalence of dementing disorders in a rural island town of Japan using a door-to-door survey focusing on various subtypes of dementia.

Methods

This study was carried out in the municipality of Ama-cho (approximately 33.5 km^2), a rural island town located 70 km from Yonago city, in the northwestern part of Japan (fig. 1). In 1904, 7 villages were integrated into Ama-son as a village, and the village was promoted to Ama-cho as a town in 1968. Three public health nurses working as permanent care providers had kept detailed information about the physical and mental health of the entire town for over 20 years. For about 30 years, board-certificated neurologists visited this town to examine dementia patients with public health nurses. Before this study, 3 public health nurses received repeated lectures regarding dementia and related disorders from board-certificated neurologists (K.W.-I., K.N). Thus, these

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0251–5350/09/0322–0101$26.00/0

Accessible online at:
www.karger.com/ned

Kenji Wada-Isoe
Department of Neurology, Institute of Neurological Sciences, Faculty of Medicine
Tottori University 36-1 Nishi-cho
Yonago, 683–8504 (Japan)
Tel. +81 859 38 6757, Fax +81 859 38 6759; E-Mail kewada@med.tottori-u.ac.jp

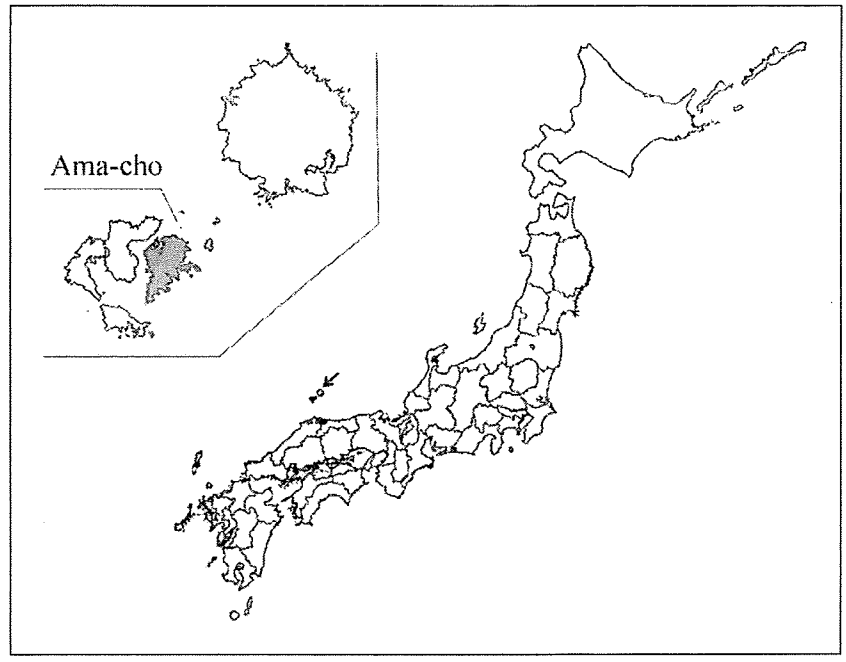

Fig. 1. Geographic location of Ama-cho. Ama-cho is a rural island town located 70 km from Yonago city (circle). The arrow indicates the direction of Oki, consisting of 3 towns and 1 village. An expanded map of Ama-cho is indicated on the left.

public health nurses were well educated and had sufficient knowledge of dementia. To be included in the study, subjects were required to be living and to be legally residing in the town on the prevalence day, 1 March 2008. The total population of Ama-cho in 2008 was 2,430 (1,145 men and 1,285 women). The number of elderly people aged 65 years and older was 943 (386 men and 557 women), or 38.4% of the total population.

In phase 1 of the study, a brief screening of all people aged 65 years and older was administered by the public health nurses in town. The screening included an interview with both subjects and their family that surveyed cognitive changes, psychiatric symptoms, personality changes, problem behaviors, activities of daily living, psychological and medical symptoms. This information was then compared with the subjects' medical history which was offered by the home doctors of the subjects. Those subjects who were suspected of having cognitive impairment sufficiently severe to impair social or professional life, were selected for phase 2 assessment.

In phase 2 of the study, the subjects who showed cognitive impairment in phase 1 were examined to confirm or exclude the presence of dementia and to classify the type of dementia. All subjects in phase 2 were examined by board-certificated neurologists. Assessment of these subjects involved a careful study of medical history, physical examination, including a drug inventory, a neurological examination, a comprehensive cognitive evaluation using the Mini-Mental State Examination [6] and the Blessed Dementia Score [7], activity of daily life evaluation with the Barthel Index [8], a psychosocial assessment of the patient's environment and routine laboratory tests. The subjects in phase 2 were asked to undergo brain computed tomography (CT) in several hospitals for diagnosis, and only a small number of subjects performed magnetic resonance images. Dementia was diagnosed by means of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised, criteria [9].

For the patients with dementia, we analyzed the dementing disease using the following criteria: (1) AD was defined according to the criteria of the National Institute of Neurological and Communication Disorders Association [10]; (2) VD was defined according to the criteria of the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences [11]; (3) dementia with Lewy bodies (DLB) was defined according to the consensus guideline for clinical diagnosis of DLB [12]; (4) Parkinson's disease dementia (PDD) was defined according to the clinical diagnostic criteria for dementia-associated Parkinson's disease [13]; (5) progressive supranuclear palsy (PSP) was defined according to the National Institute of Neurological Disorders and the Society for PSP [14]; (6) frontotemporal lobar degeneration (FTLD) was defined according to international criteria [15]. We excluded cases of cognitive decline secondary to major depression and other mental disorders like schizophrenia only if these were proven to be the main cause for cognitive decline through a psychiatric interview and medical history. Severity of dementia was assessed according to a functional assessment staging of Alzheimer's disease (FAST) [16], as follows: FAST4 = mild, FAST5 = moderate, and FAST6/7 = severe.

We examined all the subjects directly in phase 2 of the study. Prevalence and 95% confidence intervals (CIs) were calculated for all types of dementia and for specific dementing disorders.

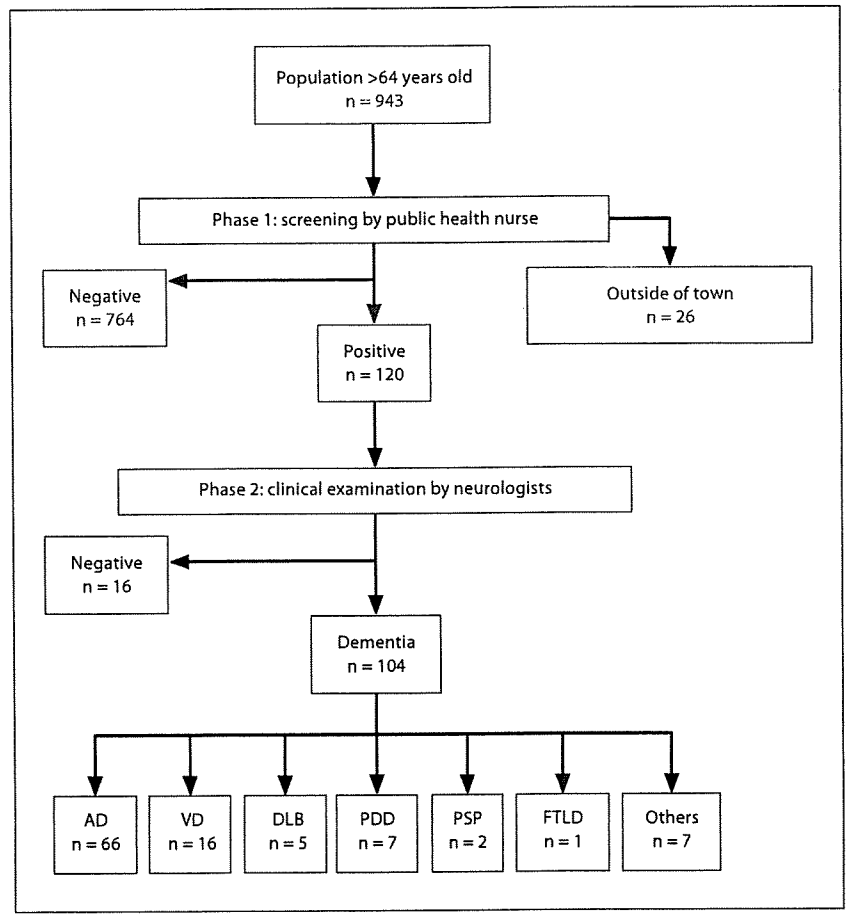

Fig. 2. General design of the door-to-door 2-phase prevalence survey in Ama-cho. The number of subjects involved in each step is shown.

Results

Figure 2 shows the general design of the door-to-door 2-phase prevalence survey. The study population included 943 subjects aged 65 years and older residing in Amacho on the prevalence day. On the prevalence day, 26 subjects (2.8%) were living outside the town.

One hundred and twenty subjects were detected as having cognitive impairment in phase 1 of the study. A total of 104 subjects (33 men, 71 women) fulfilled the diagnosis criteria of dementia, yielding a prevalence for all dementia of 11.0 cases/100 persons aged 65 years and older (95% CI 9.0–13.0). The mean age was 81.6 ± 7.1 years (range 69–93) for men and 85.0 ± 7.0 years (range 65–100) for women. Table 1 shows the number and prevalence of each dementia subtype. The age-specific prevalence of dementia increased exponentially with advancing age for women. However, for men, the prevalence was highest between 70 and 74 years. The prevalence was higher in women than in men in all ages except between 70 and 74 years. The age-adjusted prevalence for dementia by direct method in those aged 65 years and older compared with the population structure of Japan in 2004 was estimated to be 8.8 according to the data from this study.

Of the 104 demented subjects, 66 (63.5%) were diagnosed with AD (12 men, 54 women), 16 (15.4%) with VD (7 men, 9 women), 5 (4.8%) with DLB (3 men, 2 women), 7 (6.7%) with PDD (2 men, 5 women), 2 (1.9%) with PSP (2 men), and 1 (0.96%) with FTLD (1 man). Seven (6.7%) were diagnosed with mixed (1 man) or other dementia not classifiable (5 men, 1 woman). The overall prevalence was 7.0 (95% CI 5.4–8.6) for AD and 1.7 (95% CI 0.87–2.5) for VD. The prevalence of AD was 3 times higher in women than in men, while that of VD was higher in men than in women. The AD/VD ratio was 9.0 in women and 1.7