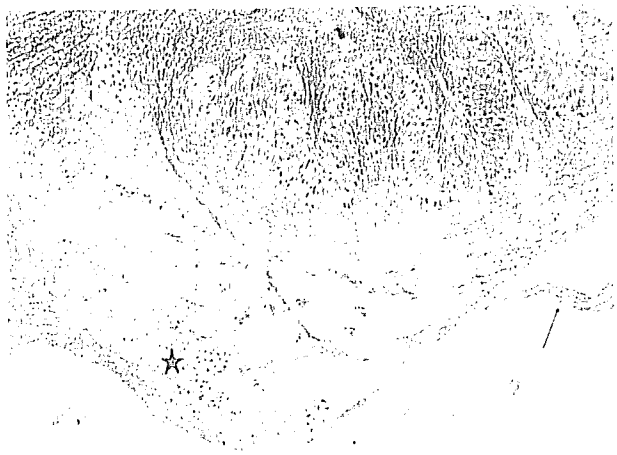

図 3　成人型 Alexander 病 51 歳例の左延髄錐体
図 2 A の枠内の拡大．延髄錐体は高度に変性して多数の小空洞を形成している．その中を走る舌下神経髄内根(ピンク矢印)と髄外根(赤矢印)は保たれている．また，壊死は錐体路にほぼ限局しており，壊死部に接する弓状核(赤★)と下オリーブ核(黄★)は保たれている．KB，×40.

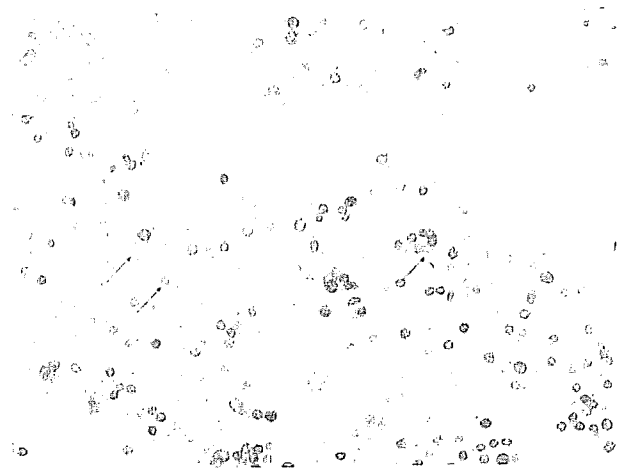

図 4　成人型 Alexander 病 51 歳例の左延髄錐体
錐体は高度に荒廃し，小空洞を形成している．変性の強さに比して Rosenthal 線維(青矢印)は少ない．HE，×400.

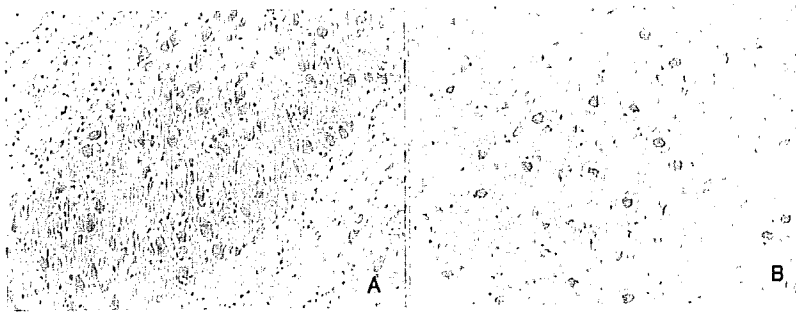

図 5　成人型 Alexander 病 51 歳例
下オリーブ核(A)のニューロン密度は対照(B)に比して明らかに高い(ニューロン間の距離が小さい)．また，成人型 AD 例下オリーブ核のニューロピルは密でグリオーシスも見られない．HE，×200.

図 6　成人型 Alexander 病 51 歳例．第 7 頸髄
錐体側索路，錐体前索路とも延髄錐体の変性に応じた変性を示している．前角の萎縮や前角大型ニューロンの脱落はない．KB，×6.

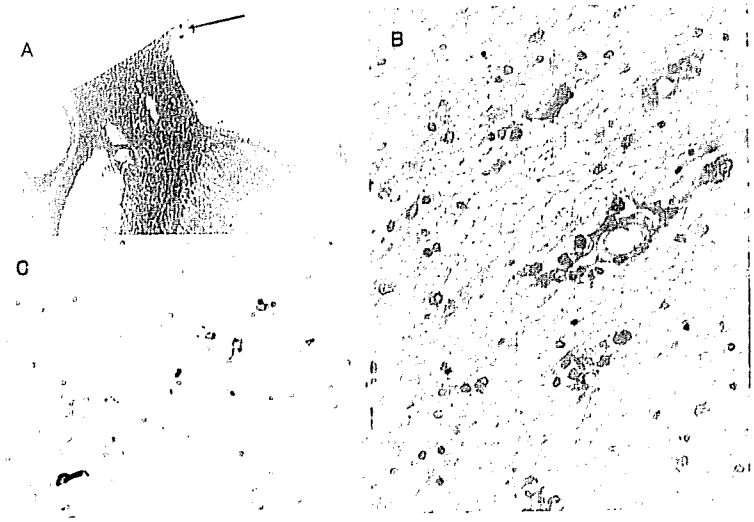

図 7　成人型 Alexander 病 51 歳例の脳梁下層(stratum subcallosum)
A) 赤矢印が脳梁下層．放線冠や内包の白質に変性は見られない．KB，×5．B) 脳梁下層には少数の Rosenthal 線維が見られる．HE，×400．C) Rosenthal 線維は辺縁がより強く染まる．抗ユビキチン抗体免疫染色，×400.

図 8　成人型 Alexander 病 51 歳例
大脳皮質の脳溝深部の軟膜下層(左上)．本例で Rosenthal 線維が最も多く見られる箇所である(右下：左上の枠の拡大)．HE，左上×10，右下×400.

日本で初めての パーキンソン病遺伝子治療

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中野（なかの）　今治（いまはる）

パーキンソン病と現在の治療法

パーキンソン病は、40～70歳で発病する脳の病気で、振戦（ふるえ）、寡動（動作が少なく、かつ遅い）、筋強剛（体が硬い）、姿勢反射障害（転びやすい）が主な症状です。通常は発病後７～８年で寝たきりとなりますが、その期間は３～15年とかなりの幅があります。

脳の中脳と呼ばれるところに黒質という場所があります。黒質の神経細胞はドパミンを作り出す細胞（ドパミン合成細胞）で、線条体というところに突起（軸索）を伸ばし（図１，2）、この突起の先端でドパミンが作られて線条体で放出されます。健常人では、ドパミン合成の第一段階として、本来ドパミン合成細胞の中に在るチロシンから、チロシン水酸化酵素 (TH)の働きによってレボドパが合成されます。このレボドパが芳香族Ｌアミノ酸脱炭酸酵素(AADC)によってドパミンに変換され、線条体で放出されて、線条体の神経細胞に作用するという仕組みになっています（図２）。ドパミンを受け取った線条体の神経細胞の一部は、最終的に視床下核という構造の神経細胞を抑制して運動が滑らかに行われるようにしています。

パーキンソン病では、この黒質のドパミン合成細

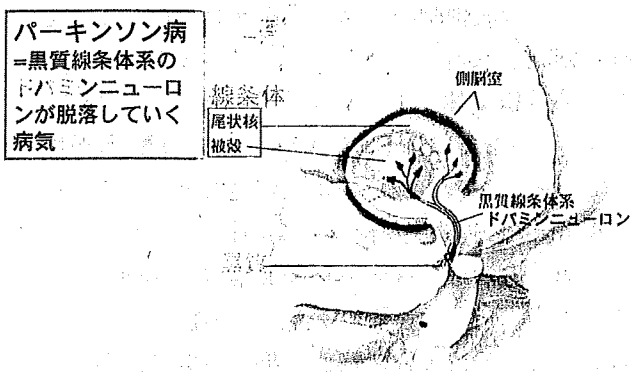

図１．人の脳の中の黒質と線条体の位置関係

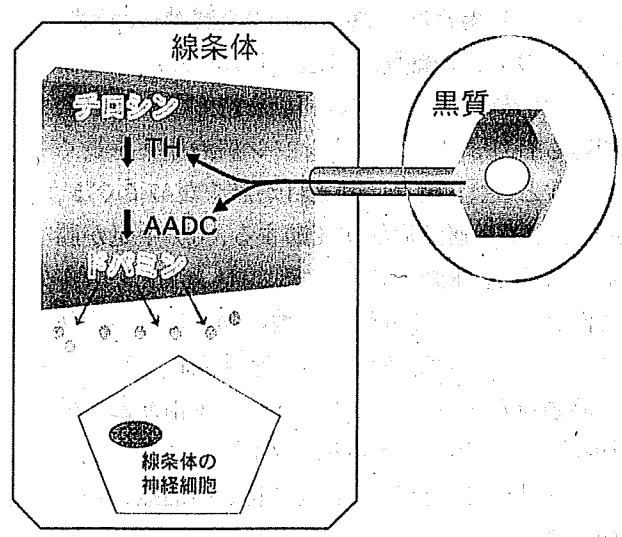

図２．健常人のドパミン合成細胞と線条体．
黒質に在るドパミン合成細胞は、線条体に突起を送り、そこでドパミンを合成して線条体に放出する．ドパミンは線条体に在る神経細胞に働く．TH：チロシン水酸化酵素、AADC：芳香族アミノ酸脱炭酸酵素．

胞が徐々に死んで行きます。そのために線条体のドパミンが足りなくなることで発病すると考えられています（図３）。線条体でドパミンが足りなくなりますと、上に述べた視床下核の神経細胞が異常に興奮し、このことが症状の出現に関係しています。私たちが行っている遺伝子治療と関係して大切なことは、パーキンソン病ではドパミンを合成する黒質の細胞は死ぬのに対して、ドパミンを受け取る線条体の神経細胞は死なないと言うことです。このことがここで述べるパーキンソン病の遺伝子治療に対する戦略の要となります。

現在、パーキンソン病治療の原則は薬物療法です。その中心となるのはドパミンの前段階の物質（前駆物質）であるレボドパです。そのほかにドパミンと類似の働きをするドパミン作動薬、放出されたドパミンの分解を防ぐモノアミン酸化酵素阻害薬、ドパミンと拮抗するアセチルコリンの作用を抑える抗コリン薬、ドパミンの放出を促すアマンタジンがあります。そして、服用したレボドパが脳に入る前に分解されるのを防ぐCOMT阻害薬（エンタカポン）も開発されました。

薬以外の治療としては、手術療法や細胞移植療法があります。手術療法の主体は深部脳刺激ですが、視床破壊術や淡蒼球破壊術なども行われます。また、細胞移植は、黒質のドパミン合成細胞と類似の働きを持つ交感神経節の神経細胞を線条体に移植する治療法です。この場合は、患者自身の交感神経節細胞を用いますので、拒絶反応は起こりません。

これらの治療法はそれぞれ利点を持っていると共に、問題も有ります。パーキンソン病治療薬を長く服用しますと、① 段々に効き目が無くなってくる、② 薬を飲んでも運動症状が変動する、③ 手足が勝手に動く不随意運動が出てくる、④ バランスを失って倒れたり、すくみ足など薬の効きにくい症状が出てくる、⑤ 幻覚妄想などの精神症状が現れるという問題点が挙げられます。また、手術療法や細胞移植療法が効果を挙げる場合も限られています。このような状況で、遺伝子治療は新しい治療方法として期待されているわけです。

ここではパーキンソン病の遺伝子治療について、私たちが今回実施した方法を中心にして述べることにします。

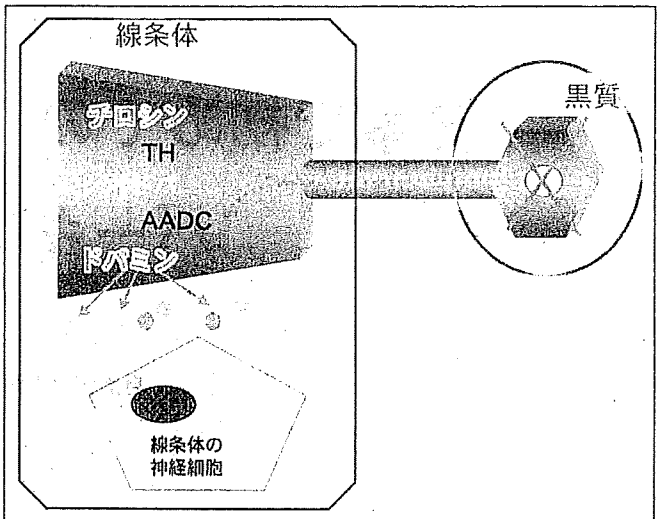

図３　パーキンソン病のドパミン合成細胞と線条体．パーキンソン病では黒質のドパミン合成細胞が死ぬために線条体でドパミンが不足する．線条体の神経細胞は生きのびている．TH：チロシン水酸化酵素、AADC：芳香族アミノ酸脱炭酸酵素．

パーキンソン病の遺伝子治療戦略

上に触れましたように、パーキンソン病発病の主なメカニズムは、① 黒質のドパミン合成細胞が脱落して、② 線条体でドパミンが足りなくなり、③ その結果、視床下核が異常に興奮した状態になることに有ると考えられます。従って、パーキンソン病の遺伝子治療の方法としては、それぞれのメカニズムを抑えることを目指した３つの方法が考えられます。

１つめは黒質のドパミン合成細胞が死ぬのを防いでやることです。この場合には、この細胞の保護作用を持っている神経栄養因子というタンパク質の遺伝子を載せたベクターを線条体に入れてやります。線条体で作られた神経栄養因子は、黒質から来ているドパミン合成細胞の突起の中を流れて行って、その神経細胞を保護すると考えられています。

２つめは線条体でドパミンを作らせることです。ドパミンの合成にはTHとAADCという酵素が関わっていますので、これらの酵素の遺伝子をベクターという遺伝子の運び屋を使って線条体に入れます。

３つめの方法は、視床下核の異常興奮を抑えてやることです。ガンマアミノ酪酸（GABA）という伝達物質には一般に神経の興奮を抑える働きが有りますので、視床下核にGABAの合成に必要なグルタミン酸脱炭酸酵素の遺伝子を視床下核に注射します

と、GABAが作られてそこの異常興奮を抑えることができます。３つの方法とも定位脳手術により、目的とする場所に遺伝子を載せたウイルスを注射します。

アデノ随伴ウイルス(AAV)をベクターとして使用

ベクターとは、治療用に使う遺伝子の運び屋です。ベクターにはいくつか種類がありますが、ウイルスベクターはこの運び屋としてウイルスを使った場合の名称です。

アデノ随伴ウイルス（AAV）は自然界に存在するありふれたウイルスのひとつで、多くの人が気づかないうちに感染しています。このウイルスはそれ自身では増えることができず、人の病気も起こしません。ウイルス由来のタンパク質の遺伝子を取り外して、空いた部分に治療用の遺伝子を載せたものが治療用ベクターです。私たちの遺伝子治療では、この空いた部分にAADCの遺伝子を入れてあります（図４）。

パーキンソン病に対する私たちの遺伝子治療の考え方

自治医大の遺伝子治療研究グループ（神経内科、遺伝子治療研究部、脳神経外科）は、パーキンソン病のモデルサルで遺伝子治療実験を行って、安全で効果が有ることを確認した後に、人での治療研究の計画を立てました。

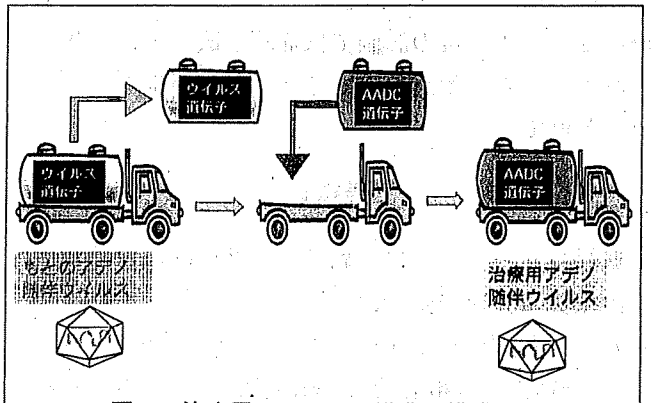

図４．治療用ベクターの構造の模式図.
自然界のアデノ随伴ウィルスは、荷台にウィルスのタンパク質を合成する遺伝子を積んだトラックにたとえられる．この遺伝子を取り除いて、ドパミンを合成する酵素の遺伝子（AADC）に積み替えたトラックが治療用ベクターである．

サルの研究では、ドパミン合成に必要なチロシン水酸化酵素（TH）、GTPシクロヒドラーゼＩ(GCH)、芳香族Lアミノ酸脱炭酸酵素（AADC）の遺伝子を線条体に注射しました（図５）。しかしながら、人に３種類の遺伝子を最初から注射するのは安全性の点で問題があります。そこで、まずAADCの遺伝子のみ線条体に注射することにしました。

AADCの遺伝子を線条体に入れて、そこの神経細胞でAADCを作ります。そうしておいてレボドパをのみますと、レボドパがその細胞の中に入って、この酵素によってドパミンに変わり、線条体に放出されます（図６，７）。作られるドパミンが多すぎると副作用が出る恐れがあります。しかし、この方法ですと、万一AADCが大量に作られすぎたとしても、服用するレボドパを減らせば作られるドパミンの量も減りますので、副作用の心配もなくなります。AADCは言わばドパミンを作る工場であり、レボドパがその原料、ドパミンが製品に相当します。工場が多く建てられすぎても材料が少なければ製品は少ししかできないのと同じ原理です。

この計画に基づいて、パーキンソン病のモデルサルでも人で行うのと同じ方法を試してみました。その結果、AADCの遺伝子だけの注射（工場を作るだけ）では効果が無いこと、そのサルにレボドパをのませること（工場に原料を供給する）で初めてドパミン（製品）が作られて効果が現れ、サルの動きが

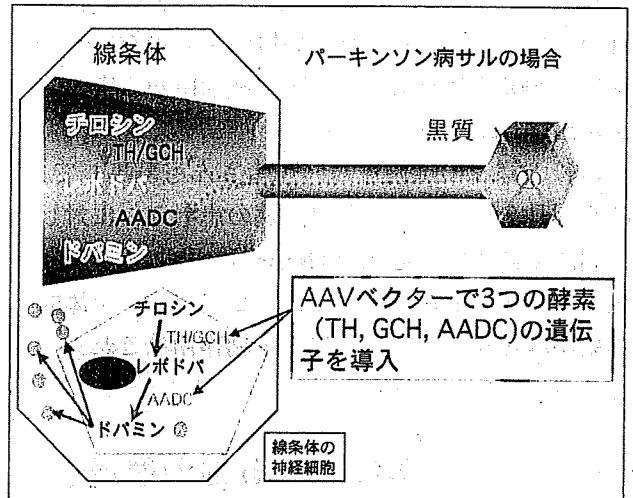

図５．パーキンソン病のモデルサルでの遺伝子治療実験.
サルの場合には３つの酵素（TH：チロシン水酸化酵素、GCH：GTPシクロヒドラーゼ Ⅰ、AADC：芳香族アミノ酸脱炭酸酵素）の遺伝子を同時に入れて安全で効果が有ることを確認した．

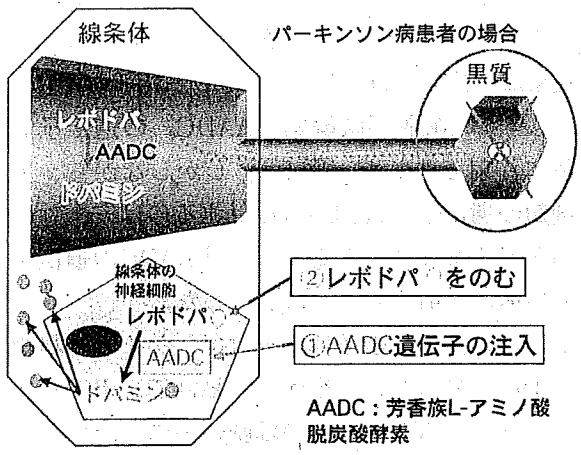

図6．パーキンソン病の遺伝子治療の第一段階．AADCの遺伝子のみを線条体に注射し、レボドパをのんでドパミンを作らせる．

良くなることが確認されました。

パーキンソン病に対する私たちの遺伝子治療の実施

以上のような考え方に立って、進行したパーキンソン病を対象とした遺伝子治療計画を作り、まず、自治医科大学附属病院遺伝子治療臨床研究審査委員会に提出して、十分な審査を受けました。そこで研究計画が認められた後に、今度は厚生労働省の厚生科学審議会科学技術部会に計画書を申請し、そこでの審議を経た後にパーキンソン病遺伝子治療臨床研究作業委員会という会に降ろされて、本格的な審議が行われました。このように何段階もの審査を受けた後に、2006年10月31日、厚生労働大臣から実施許可証が出ました。

その後、様々の準備をし、患者さんも募集して、2007年5月7日にパーキンソン病の患者さんに対して、国内で初めての遺伝子治療を行いました。現在予定した6例の治療を終了したところです。全体的に効果がみられ、ベクターによる副作用はこれまでのところ出ておりません。

パーキンソン病に対する他の遺伝子治療法

先に、パーキンソン病に対する遺伝子治療の考え方には大きく3つ有ることを述べました。私たち以外に、パーキンソン病の遺伝子治療が実際に行われ

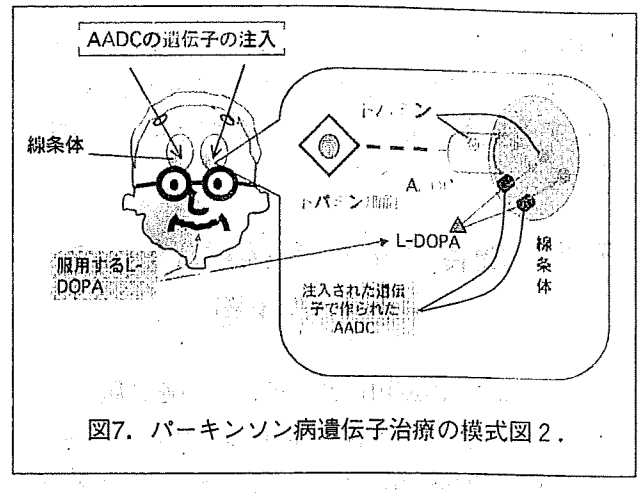

図7．パーキンソン病遺伝子治療の模式図2．

ているのはアメリカのみで、先に触れた3つの方法が行われています。3つの遺伝子治療ともベクターとしてアデノ随伴ウイルスを用いています。注入はいずれも定位脳手術で行っています。

私たちと同じ方法で行っているのは、カリフォルニア大学サンフランシスコ医療センターで、ここでは既に9例の治療が行われています。

もう一つの治療では、視床下核の異常興奮を抑えるために片側にのみグルタミン酸脱炭酸酵素（GAD）の遺伝子を注射します。この方法は、2003年にコーネル大学で開始され、現在最初の12例が終了してイギリスの医学雑誌ランセットに論文が発表されました。それによりますと、治療側の手足（注射と反対側の手足）で1年後でも症状の改善が認められ、PETを使って遺伝子の働きが確認されたとのことです。

3番目の治療法は、神経栄養因子の一つであるニュールトリン（NTN）という物質の遺伝子を両側の線条体に注入する方法です。これまで12例が治療を受け、1年後の評価では症状が改善いたと報告されましたが、治験第Ⅱ相では有意差が出なかったと言われています。

最後に

進行したパーキンソン病では、特効薬はなく新規の治療法の開発が望まれています。遺伝子治療はまだ始まったばかりですが、さらに改良が加えられることは確実で、期待される治療法になると考えられます。

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

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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

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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.

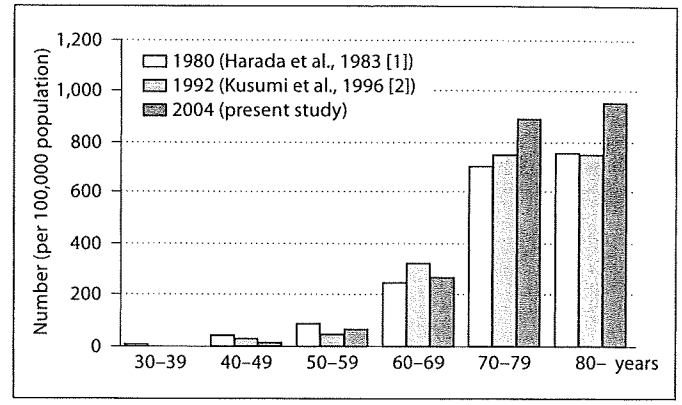

Fig. 1. Comparison of age-specific prevalence of PD. The crude prevalence tended to decrease in those less than 50 years of age, and to increase in those greater than 70 years of age.

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

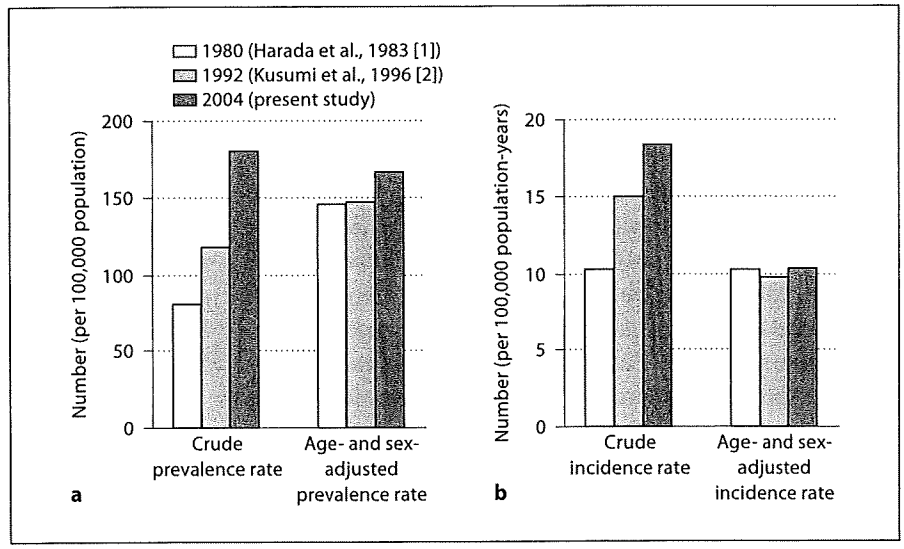

Fig. 2. Comparison of prevalence and incidence of PD. **a** The age- and sex-adjusted prevalence was significantly increased (adjusted to the Japanese population in 2004). **b** The age- and sex-adjusted incidence was not changed (adjusted to the population of Yonago in 1980).

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.

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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.

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

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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

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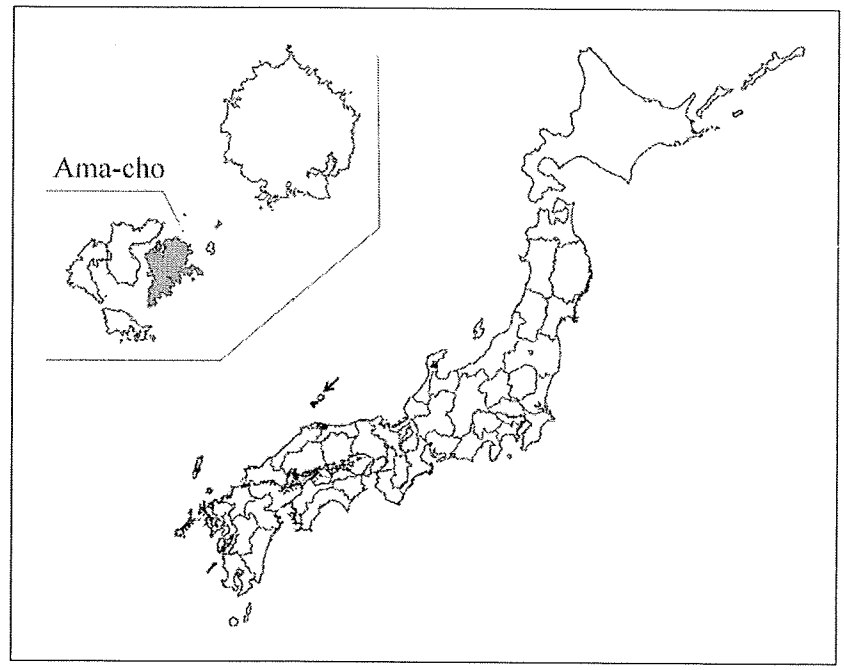

Fig. 1. Geographic location of Ama-cho. Ama-cho is a rural island town located 70 km from Yonago city (circle). The arrow indicates the direction of Oki, consisting of 3 towns and 1 village. An expanded map of Ama-cho is indicated on the left.

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.

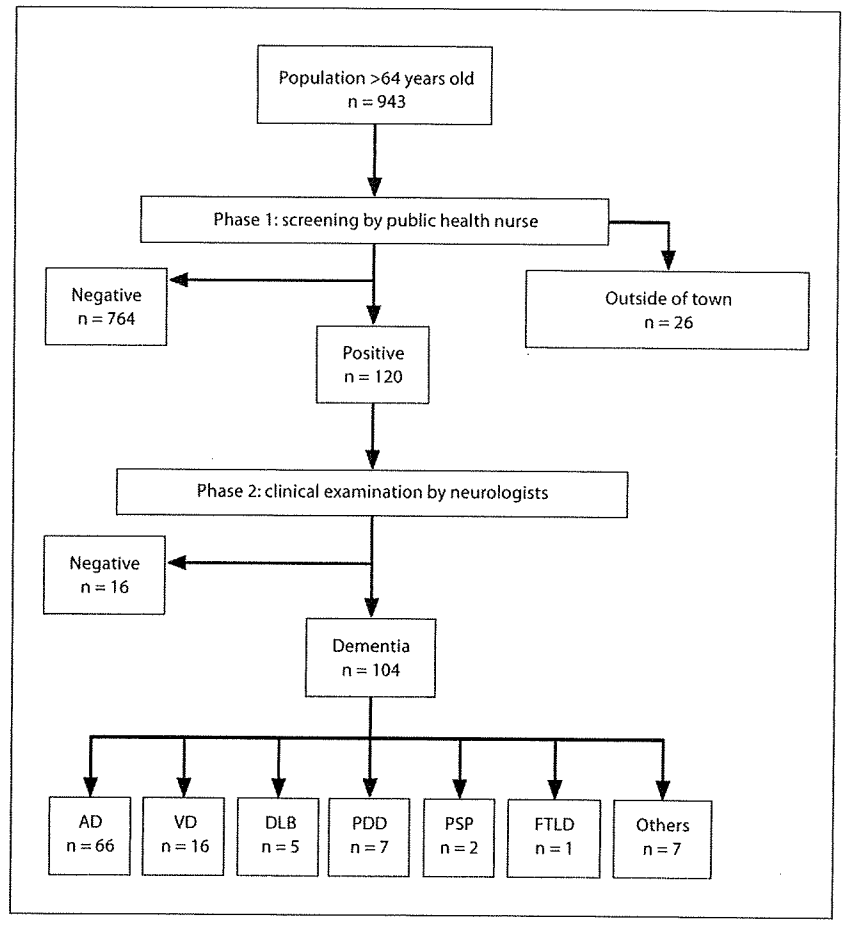

Fig. 2. General design of the door-to-door 2-phase prevalence survey in Ama-cho. The number of subjects involved in each step is shown.

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

Table 1. Age- and sex-specific prevalence of dementia

	Population at risk	All types		AD		VD		DLB		PDD		PSP		FTLD		Others	
		cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence	cases	prevalence
Both sexes																	
65–69 years	178	2	1.1	–	–	1	0.56	–	–	1	0.56	–	–	–	–	–	–
70–74 years	206	10	4.9	4	1.9	4	1.9	–	–	–	–	–	–	1	0.49	1	0.49
75–79 years	226	19	8.4	10	4.4	4	1.8	1	0.44	1	0.44	–	–	–	–	3	1.3
80–84 years	161	22	13.7	16	9.9	2	1.2	1	0.62	–	–	2	1.2	–	–	1	0.62
85–89 years	114	27	23.7	18	15.8	1	0.88	3	2.6	4	3.5	–	–	–	–	1	0.88
90– years	58	24	41.4	18	31.0	4	6.9	–	–	1	1.72	–	–	–	–	1	1.7
Total	943	104	11.0	66	7.0	16	1.7	5	0.53	7	0.74	2	0.21	1	0.11	7	0.74
Men																	
65–69 years	87	1	1.2	–	–	–	–	–	–	1	1.2	–	–	–	–	–	–
70–74 years	90	6	6.7	2	2.2	2	2.2	–	–	–	–	–	–	1	1.1	1	1.1
75–79 years	99	8	8.1	2	2.0	2	2.0	1	1.0	–	–	–	–	–	–	3	3.0
80–84 years	52	6	11.5	2	3.8	2	3.8	–	–	–	–	2	3.9	–	–	–	–
85–89 years	43	7	16.3	2	4.7	1	2.3	2	4.7	1	2.3	–	–	–	–	1	2.3
90– years	15	5	33.3	4	26.7	–	–	–	–	–	–	–	–	–	–	1	6.7
Total	386	33	8.5	12	3.1	7	1.8	3	0.78	2	0.52	2	0.52	1	0.26	6	1.6
Women																	
65–69 years	91	1	1.1	–	–	1	1.1	–	–	–	–	–	–	–	–	–	–
70–74 years	116	4	3.4	2	1.7	2	1.7	–	–	–	–	–	–	–	–	–	–
75–79 years	127	11	8.7	8	6.3	2	1.6	–	–	1	0.79	–	–	–	–	–	–
80–84 years	109	16	14.7	14	12.8	–	–	1	0.92	–	–	–	–	–	–	1	0.92
85–89 years	71	20	28.2	16	22.5	–	–	1	1.4	3	4.2	–	–	–	–	–	–
90– years	43	19	44.2	14	32.6	4	9.3	–	–	1	2.3	–	–	–	–	–	–
Total	557	71	12.7	54	9.7	9	1.6	2	0.36	5	0.90	–	–	–	–	1	0.18

Prevalence = cases/100.

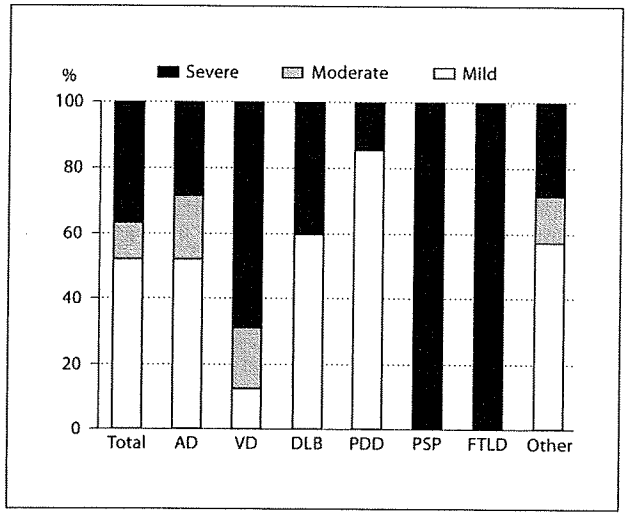

Fig. 3. Severity of subtypes of dementia.

in men. The prevalence was 0.53 (95% CI 0.07–0.99) for DLB and 0.74 (95% CI 0.19–1.3) for PDD. The AD/DLB ratio in both sexes was 13.2. The severity of dementia according to FAST is shown in figure 3. Fifty-four (52.0%) were at the mild stage, 12 (11.5%) at the moderate stage, and 38 (36.5%) were at the severe stage. In AD, most subjects were at the mild stage; however, in VD, most subjects were at the severe stage. Fifty-four (52%) were living in their home and 50 (48%) were living in a nursing home in town.

Discussion

We investigated the prevalence of dementia in an isolated rural island community in western Japan. We selected this town for the following reasons: (1) the public health nurses working as the sole permanent care providers have been keeping detailed information about the physical and mental health of the entire town for over 20

years; (2) active collaboration was offered by family doctors in the town; (3) this town is a rural island with a stable population, and only a few demented subjects move to nursing homes in other areas.

Our study showed that the prevalence of all types of dementia in the elderly population aged 65 years and older was 11.0 in a rural community in Japan. This finding is higher than that of previous Japanese reports showing a prevalence of 3.8–8.5 [3–5, 17–19]. There are some possible reasons for the higher prevalence of dementia found in our study. The first is the relatively higher proportion of subjects in the population aged 65 years and older in the town studied. Second, we surveyed all the demented subjects including those instituted in the nursing home in town, where severely demented subjects are living. Thus, our study indicated a relatively higher prevalence of subjects with severe dementia. Third, we achieved a very high response rate in this survey, due to the outstanding contribution of the public health nurses.

In agreement with recent epidemiological studies in Japan, our study showed that AD is the most common and VD is the second most common subtype of dementia amongst all types of dementia in elderly people [3–5,17, 19]. We also examined the prevalence of subtypes of dementia other than AD and VD. The prevalence was 0.53 for DLB in our study. Some epidemiologic data on DLB are available from a community-based survey. The prevalence of DLB in the general population is reported to be from 0 to 5 [20]. Yamada et al. [17] reported that the prevalence of DLB in Japan among subjects aged 65 years and older was 0.1. Yokota et al. [21] reported the AD/DLB ratio to be 12.9 in their study based on a hospital memory clinic in Japan. The AD/DLB ratio in our study was 13.2, which was consistent with their study. We also examined the prevalence of PDD in the same community. Although several studies found a prevalence of DLB or PDD, few have reported a simultaneous prevalence in a community. DLB and PDD share many pathological and clinical features [22]. The time course of the symptoms and presenting features primarily differentiate these disorders. In this study, the 1-year rule between the onset of dementia and parkinsonism was adapted to distinguish between DLB and PDD. The PDD patients were reliably diagnosed amongst PD patients who had been diagnosed by the UK PD Brain Bank clinical diagnostic criteria [23]. In our study, the prevalence of PDD was 0.74, which was higher than that of DLB. After a systematic review, Arsland et al. [24] reported a 0.2–0.5 prevalence of PDD in the general population. Our results appear to be consistent with this finding.

Only 1 subject was diagnosed as having FTLD in our study. A high frequency of FTLD patients has been reported amongst subjects aged <65 years, but not in subjects aged 65 years and older in Western countries [25, 26]. After their hospital-based study in Japan, Yokota et al. [21] reported that FTLD was the second most common neurodegenerative dementia following AD amongst those with early-onset dementia, but it was very rare amongst late-onset patients. Among 3,715 subjects >65 years of age, Yamada et al. [17] found that none were diagnosed with FTLD, and Ikeda et al. [18] reported only 2 subjects with FTLD among 1,438 subjects aged >64 years in their community-based study in Japan. Our data are consistent with these community-based studies. There is a lack of valid and reliable methods for screening the core clinical features by which FTLD is usually identified, so FTLD can be difficult to diagnose in the community.

This study is a door-to-door, 2-phase design based on phase 1 screening by highly educated public health nurses and on phase 2 diagnosis by a neurologist. Some limitations of this study have to be considered. One important limitation was the relatively small size of the population surveyed, and our estimations of subtypes of dementia are based on a small number of cases. Second, we mainly evaluated brain imaging of the subjects by CT scan; however, magnetic resonance imaging detects abnormal findings more sensitively than CT. Third, although all diagnoses in this study were made according to the most recent clinical diagnostic criteria, no patients were neuropathologically diagnosed with subtypes of dementia.

In conclusion, we showed the prevalence of dementia in the elderly population aged 65 years and older in a rural area in Japan to be 11.0 cases/100 population, which is higher than that found by previous epidemiological studies in Japan.

Acknowledgments

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References

1 Ueda K, Kawano H, Hasuo Y, Fujishima M: Prevalence and etiology of dementia in a Japanese community. Stroke 1992;23:798–803.
2 Hatada K, Okazaki Y, Yoshitake K, Takada K, Nakane Y: Further evidence of westernization of dementia prevalence in Nagasaki, Japan, and family recognition. Int Psychogeriatr 1999;11:123–138.
3 Urakami K, Adachi Y, Wakutani Y, Isoe K, Ji Y, Takahashi K, Nakashima K: Epidemiologic and genetic studies of dementia of the Alzheimer type in Japan. Dement Geriatr Cogn Disord 1998;9:294–298.
4 Shiba M, Shimogaito J, Kose A, Fujiuchi S, Nishiyama H, Yoshimasu F, Asai T, Rocca WA: Prevalence of dementia in the rural village of Hanazono-mura, Japan. Neuroepidemiology 1999;18:32–36.
5 Wakutani Y, Kusumi M, Wada K, Kawasima M, Ishizaki K, Mori M, Mori N, Ijiri T, Adachi Y, Ashida Y Kuno N, Urakami K, Takeshima T, Nakashima K: Longitudinal changes in the prevalence of dementia in a Japanese rural area. Psychogeriatrics 2007;7:150–154.
6 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
7 Blessed G, Tomlinson BE, Roth M: The association between quantitative measures of dementia and of senile change in the cerebral gray matter of elderly subjects. Br J Psychiatry 1968;114:797–811.
8 Granger CV, Rewis LS, Peters NC, Sherwood CC, Barrett JE: Stroke rehabilitation – analysis of repeated Barthel index measures. Arch Phys Med Rehabil 1979;60:14–17.
9 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, American Psychiatric Association, 1994.
10 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
11 Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennett DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, DeCarli C, Culebras A, Korczyn AD, Bogousslavsky J, Hartmann A, Scheinberg P: Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
12 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, Consortium on DLB: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
13 Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B: Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22:1689–1707.
14 Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47:1–9.
15 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51: 1546–1554.
16 Reisberg B: Dementia: a systematic approach to identifying reversible causes. Geriatrics 1986;41:30–46.
17 Yamada T, Hattori H, Miura A, Tanabe M, Yamori Y: Prevalence of Alzheimer's disease, vascular dementia and dementia with Lewy bodies in a Japanese population. Psychiatry Clin Neurosci 2001;55:21–25.
18 Ikeda M, Hokoishi K, Maki N, Nebu A, Tachibana N, Komori K, Shigenobu K, Fukuhara R, Tanabe H: Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. Neurology 2001;57:839–844.
19 Meguro K, Ishii H, Yamaguchi S, Ishizaki J, Shimada M, Sato M, Hashimoto R, Shimada Y, Meguro M, Yamadori A, Sekita Y: Prevalence of dementia and dementing diseases in Japan: the Tajiri project. Arch Neurol 2002; 59:1109–1114.
20 Zaccai J, McCracken C, Brayne C: A systematic review of prevalence and incidence studies of dementia with Lewy bodies. Age Ageing 2005;34:561–566.
21 Yokota O, Sasaki K, Fujisawa Y, Takahashi J, Terada S, Ishihara T, Nakashima H, Kugo A, Ata T, Ishizu H, Kuroda S: Frequency of early and late-onset dementias in a Japanese memory disorders clinic. Eur J Neurol 2005; 12:782–790.
22 McKeith IG, Burn D: Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia; in DeKosky ST (ed): Neurologic Clinics. Philadelphia, Saunders, 2000, pp 865–883.
23 Hughes AJ, Daniel SE, Blankson S, Lees AJ: A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 1993;50: 140–148.
24 Aarsland D, Zaccai J, Brayne C: A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord 2005;20: 1255–1263.
25 Vraamark Elberling T, Stokholm J, Høgh P, Waldemar G: Diagnostic profile of young and middle-aged memory clinic patients. Neurology 2002;59:1259–1262.
26 Ratnavalli E, Brayne C, Dawson K, Hodges JR: The prevalence of frontotemporal dementia. Neurology 2002;58:1615–1621.

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Assessment of dementia in patients with multiple system atrophy

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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

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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

