were identified as having early onset (age <65 years) of the disease, and 386 (115 males and 271 females) were identified as late-onset cases (age ≥65 years). The subjects' family background information was also obtained from their spouses or relatives, and the family histories of AD patients who had first-degree relatives with AD were considered positive. The cases identified as familial AD numbered 35, while 443 were identified as sporadic; the family history could not be ascertained for the remaining 9 AD subjects because of the uncertainty of the information.

The control group consisted of 471 elderly, unrelated Japanese (150 males and 321 females; mean age 75.2 ± 6.1 years). To evaluate their cognitive function, we administered the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and excluded subjects whose MMSE scores were less than 25.

Genotyping

DNA was extracted from peripheral blood according to standard procedures. A pair of primers (forward, 5′-ATC CGA GGA CAA GGT GGC-3′; and reverse, 5′-CCT CAT GGA CAT GTT TGC AG-3′) was generated. Polymerase chain reaction (PCR) amplification was performed using 2.0 units of AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, CA) and 10 pmol of each primer according to the manufacturer's instructions (final volume, 20 µl). After activation of AmpliTaq Gold DNA polymerase for 9 min at 95°C, we subjected the reaction mixture to 35 cycles (94°C, 60°C, and 72°C for 30 s each), followed by a final extension at 72°C for 10 min. The 300-bp amplification product was purified by ethanol precipitation and digested with 10 units of *Pml I* at 37°C overnight. The resulting DNA fragments were separated on a 2% agarose gel and visualized with ethidium bromide staining. The A allele of BDNF G196A polymorphism was not digested by *Pml I*, but the G allele showed two bands, at 180 bp and 120 bp.

The BDNF C270T polymorphism was genotyped by a slight modification of a procedure described elsewhere (Kunugi et al., 2001). Briefly, we generated a pair of primers (forward, 5′-CAG AGG AGC CAG CCC GGT GCG-3′; reverse, 5′-CTC CTG CAC CAA GCC CCA TTG-3′). We performed PCR using HotStarTaq DNA polymerase (QIAGEN, Valencia, CA) and 10 pmol of each primer in a final volume of 50 µl. After activation of HotStarTaq DNA polymerase for 15 min at 95°C, we subjected the reaction mixture to 35 cycles of PCR (94°C for 60 s, 64°C for 60 s, and 72°C for 30 s each), followed by a final extension at 72°C for 10 min. The 233-bp amplification product was purified by ethanol precipitation and digested with 10 units of *Hinf I* at 37°C overnight. The resulting DNA fragments were separated on a 13.3% polyacrylamide gel and visualized with ethidium bromide staining.

ApoE genotypes were determined by a PCR-RFLP procedure described by Wenham et al. (1991).

Statistics

Statistical calculations were done using a SAS package (Statistical Analysis System, SAS Institute, Cary, NC) to detect significant differences with the chi-square test and Student's *t*-test. Odds ratios (OR) with 95% confidence interval (CI) were calculated to compare the groups' allele frequencies. We used the Power and Precision program (Borenstein et al., 1997) to calculate the study's statistical power. To assess whether linkage disequilibrium exists between the two polymorphisms of the BDNF gene, we performed statistical tests using a previously described method (Matsushita et al., 2001) and the actual calculations and its statistical significance were made using the ASSOCIAT program downloaded form the website of Dr. J. Ott (http://linkage.rockefeller.edu/software/linkage).

Results

Because of the proximity of the G196A and C270T polymorphisms in the BDNF gene, our effort to determine linkage disequilibrium between the two

Table 1. Linkage disequilibrium between the C270T and G196A polymorphisms of the BDNF gene in control subjects

G196A genotypes	C270T genotypes		
	CC	CT	TT
AA	98	0	0
AG	209	14	0
GG	131	19	0

loci showed incomplete disequilibrium in control subjects ($D=0.0156$, $\chi^2=20.474$, $df=4$, $p<0.001$) (Table 1). Therefore, we compared the distribution of each polymorphism separately.

The genotypes of the G196A polymorphisms were in Hardy-Weinberg equilibrium in controls as well as in AD subjects (Table 2). The frequencies of the GG and GA genotypes and the G allele of the G196A polymorphism were significantly higher in AD subjects than in controls (Table 2). When we set the true difference in GG genotype frequency between AD and controls in this comparison at 0.16 ($0.65-0.49$), to coincide with that in a previous report (Ventriglia et al., 2002), we achieved a statistical power of 100%. The odds ratio of the G allele for AD was 1.23 (95% CI, 1.02–1.47). Because the GG and GA genotypes were overrepresented in AD subjects, we combined these genotypes and compared the combined frequencies in AD patients and controls. The risk for AD in the presence of both GG and GA genotypes (OR) was 1.59 (95% CI, 1.13–2.23), differing significantly ($\chi^2=7.33$, $P=0.0068$) from that of the risk for AD posed by the G allele.

When we divided our AD subjects according to their ApoE4 status, the presence or absence of family history of AD, and age at onset and then compared the genotype and allele frequencies of the G196A polymorphism, we found no significant differences in the distribution of G196A genotypes and alleles in AD patients with and without the ApoE4 carrier, with and without an AD-positive family history, or with early-onset versus late-onset AD.

The genotypes of both C270T polymorphisms were in Hardy-Weinberg equilibrium in controls as well as in AD subjects (Table 3). Because we found the TT genotype in only one sporadic AD subject, we combined the CT and TT genotypes for further analysis. There were no significant differences in C270T polymorphism distribution between overall AD and control subjects. Setting the true difference in T-allele frequency between the AD cases and controls at 0.04 ($0.06-0.02$), as in a previously reported study (Kunugi et al., 2001), yielded a statistical power of 99%.

Subsequent comparison of the AD subjects' C270T genotype and allele distributions by ApoE4 status, family history of dementia, and age at AD onset showed that the AD subjects who lacked ApoE4 and those who had a family history of AD had significantly higher frequencies of the T allele and of the CT (and TT) genotypes.

Table 2. Genotype and allele frequencies of the BDNF gene G196A polymorphism in Alzheimer's disease cases and controls

	Alzheimer's disease cases							Controls (n = 471) N (%)
	ApoE4 (+) (n = 248) N (%)	ApoE4 (−) (n = 239) N (%)	Family history (+) (n = 35) N (%)	Family history (−) (n = 443) N (%)	Early onset (<65 yr) (n = 101) N (%)	Late onset (≥65 yr) (n = 386) N (%)	Total (n = 487) N (%)	
Genotype								
GG	88 (35.5)	83 (34.7)	10 (28.6)	159 (35.9)	34 (33.7)	137 (35.5)	171 (35.1)	150* (31.9)
GA	126 (50.8)	121 (50.6)	21 (60.0)	220 (50.0)	52 (51.5)	195 (50.5)	247 (50.7)	223 (47.4)
AA	34 (13.7)	35 (14.6)	4 (11.4)	64 (14.5)	15 (14.9)	54 (14.0)	69 (14.2)	98 (20.8)
Allele								
G	302 (60.9)	287 (60.0)	41 (58.6)	538 (60.7)	120 (59.4)	469 (60.8)	589 (60.5)	523† (55.5)
A	194 (39.1)	191 (40.0)	29 (41.4)	348 (39.3)	82 (40.6)	303 (39.3)	385 (39.5)	419 (44.5)

* Total AD vs. control: $df = 2$, $\chi^2 = 7.37$, $p = 0.0251$. † Total AD vs. control: $df = 1$, $\chi^2 = 4.82$, $p = 0.028$

Table 3. Genotype and allele frequencies of the BDNF gene C270T polymorphism in Alzheimer's disease cases and controls

	Alzheimer's disease cases							Controls (n = 471) N (%)
	ApoE4 (+) (n = 248) N (%)	ApoE4 (−) (n = 239) N (%)	Family history (+) (n = 35) N (%)	Family history (−) (n = 443) N (%)	Early onset (<65 yr) (n = 101) N (%)	Late onset (≥65 yr) (n = 386) N (%)	Total (n = 487) N (%)	
Genotype								
CC	238 (96.0)	219 (91.6)	30 (85.7)	419 (94.6)	98 (97.0)	359 (93.0)	457 (93.8)	438 (93.0)
CT or TT	10 (4.0)	20* (8.4)	5 (14.3)	24† (5.4)	3 (3.0)	27 (7.0)	30 (6.2)	33 (7.0)
Allele								
C	486 (98.0)	457‡ (95.6)	65 (92.9)	861§ (97.2)	199 (98.5)	744 (96.4)	943 (96.8)	909 (96.5)
T	10 (2.0)	21 (4.4)	5 (7.1)	25 (2.8)	3 (1.5)	28 (3.6)	31 (3.2)	33 (3.5)

*ApoE4 (+) vs. ApoE4 (−): $df = 1$, $\chi^2 = 3.96$, $p = 0.0466$. †Family history (+) vs. family history (−): $df = 1$, $\chi^2 = 4.48$, $p = 0.0344$. ‡ApoE4 (+) vs. ApoE4 (−): $df = 1$, $\chi^2 = 4.46$, $p = 0.0346$. §Family history (+) vs. family history (−): $df = 1$, $\chi^2 = 3.96$, $p = 0.0459$.

Discussion

This study showed that (1) the C270T and G196A BDNF gene polymorphisms are in incomplete disequilibrium. (2) The frequencies of the GG and GA genotypes and the G allele of the G196A polymorphism were significantly higher in our AD subjects than in our control subjects. (3) The distribution of the C270T polymorphism did not differ significantly between AD and control subjects. (4) The frequency of the T allele of the C270T polymorphism was significantly higher in both ApoE4-positive and family history-negative AD.

None of the known previous studies of the G196A and C270T polymorphisms of the BDNF gene examined both simultaneously. In the first of the three studies, Kunugi et al. (2001) found that the frequency of the T allele of the C270T polymorphism (7.6%) was significantly higher in late-onset AD cases than in controls. The 2.1% frequency of the T allele in their control subjects (Kunugi et al., 2001) is comparable with the frequency of the T allele in our controls (3.5%).

In the second study, examination of the association between C270T polymorphism and AD by Riemenschneider et al. (2002) showed a significantly higher frequency of the T allele in AD cases in general (6.2%) than in controls. This association was more prevalent in AD patients lacking ApoE4, especially in early-onset cases. We could not replicate the Riemenschneider study's overall association between AD and the C270T polymorphism, nor could we find the reported effect of the T allele on the onset of disease in our AD subjects. (The mean age at onset for our cases with the CC genotype was 70.4 ± 8.5 years; for those with the CT genotype, it was 72.0 ± 9.2 years.) Nevertheless, our results do support the C270T association with AD in subjects lacking ApoE4. Although we found a higher frequency of the T allele in AD cases with family history of dementia, only a few of our cases had AD in their family history. Therefore, these results remain to be confirmed in a larger sample.

Only the third of the three previous studies examined the association between the G196A polymorphism and AD. Ventriglia et al. (2002) showed a significantly higher frequency of the GG genotype of the G196A polymorphism in AD subjects than in controls, regardless of ApoE4 status. There was a nonsignificant trend toward a higher frequency of the G allele of the G196A polymorphism in cases than in controls (Ventriglia et al., 2002). The results of our study using a much larger sample support these findings.

There are three potential explanations for the (relatively weak) association we found: First, a recent study by Egan et al. (2003) suggested that the G196A polymorphism is functional, and that this polymorphism affects intracellular distribution, packaging, and release of the BDNF protein in vitro. They reported that the polymorphism had significant effects on verbal episodic memory, hippocampal activation, and measures of hippocampal neuronal integrity and synaptic abundance (Egan et al., 2003). Given the recent finding by Michalski and Fahnestock (2003) that proBDNF protein is lower in the AD parietal cortex, the G196A polymorphism might play some role in the development of AD, by altering the expression of proBDNF. However, using functional magnetic resonance imaging (fMRI) and ^{1}H magnetic resonance spectroscopic imaging

(MRSI), Egan and colleagues showed that the A allele of the G196A polymorphism was associated with poorer episodic memory, abnormal hippocampal activation, and lower hippocampal N-acetyl aspartate levels (NAA) in healthy subjects. Our results suggesting association of the G allele of the G196A polymorphism with AD are inconsistent with those findings. Moreover, because the results of the Egan study were obtained from healthy subjects, those study findings do not explain the pathophysiology of AD. Thus, the role of the G196A polymorphism in the pathophysiology of AD remains unknown.

The second possible explanation is that this polymorphism may be in linkage disequilibrium with other polymorphisms elsewhere in the gene, demonstrating biologically relevant variability. This seems unlikely, however, inasmuch as an extensive search has failed to identify common polymorphisms accompanying amino acid replacement in this gene (Egan et al., 2003; Weese-Mayer et al., 2002). Finally, the third explanation is the possibility that this polymorphism is in linkage disequilibrium with a genetic variation of another gene located near the BDNF gene.

Although with sufficient statistical power we found a positive association between BDNF gene polymorphisms and AD, our findings need to be replicated in still larger, independent samples, or in family-based samples, to reach firm conclusions.

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References

Borenstein M, Rothstein H, Cohen J (1997) Power and precision. Lawrence Erlbaum, Englewood, NJ

Durany N, Michel T, Kurt J, Cruz-Sanchez FF, Cervas-Navarro J, Riederer P (2000) Brain-derived neurotrophic factor and neurotrophin-3 levels in Alzheimer's disease brains. Int J Dev Neurosci 18: 807–813

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112: 257–269

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state." A practical method for grading the cognitive state of patients for the clinicians. J Psychiatr Res 12: 189–198

Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349: 704–706

Hock C, Heese K, Hulette C, Rosenberg C, Otten U (2000) Region-specific neurotrophin imbalances in Alzheimer disease: decreased levels of brain-derived neurotrophic factor and increased levels of nerve growth factor in hippocampus and cortical areas. Arch Neurol 57: 846–851

Holsinger RM, Schnarr J, Henry P, Castelo VT, Fahnestock M (2000) Quantification of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease. Brain Res Mol Brain Res 76: 347–354

Kunugi H, Ueki A, Otsuka M, Isse K, Hirasawa H, Kato N, Nabika T, Kobayashi S, Nanko S (2001) A novel polymorphism of the brain-derived neurotrophic factor (BDNF) gene associated with late-onset Alzheimer's disease. Mol Psychiatry 6: 83–86

Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu YH, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE (1995) Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 269: 973–977

Matsushita S, Arai H, Yuzuriha T, Kato M, Matsui T, Urakami K, Higuchi S (2001) No association between DLST gene and Alzheimer's disease or Wernicke-Korsakoff syndrome. Neurobiol Aging 22: 569–574

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) 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 34: 939–944

Michalski B, Fahnestock M (2003) Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Brain Res Mol Brain Res 111: 148–154

Narisawa-Saito M, Wakabayashi K, Tsuji S, Takahashi H, Nawa H (1996) Regional specificity of alterations in NGF, BDNF and NT-3 levels in Alzheimer's disease. Neuroreport 7: 2925–2928

Pringle AK, Sundstrom LE, Wilde GJ, Williams LR, Iannotti F (1996) Brain-derived neurotrophic factor, but not neurotrophin-3, prevents ischaemia-induced neuronal cell death in organotypic rat hippocampal slice cultures. Neurosci Lett 211: 203–206

Riemenschneider M, Schwarz S, Wagenpfeil S, Diehl J, Muller U, Forstl H, Kurz A (2002) A polymorphism of the brain-derived neurotrophic factor (BDNF) is associated with Alzheimer's disease in patients lacking the apolipoprotein E epsilon4 allele. Mol Psychiatry 7: 782–785

Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ (1993) Association of apolipoprotein E allele ε 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43: 1467–1472

Seidah NG, Benjannet S, Pareek S, Chretien M, Murphy RA (1996) Cellular processing of the neurotrophin precursors of NT3 and BDNF by the mammalian proprotein convertases. FEBS Lett 379: 247–250

Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Foncin JF, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, Da Silva HAR, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St George-Hyslop PH (1995) Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 375: 754–760

Terry RD (1994) Neuropathological changes in Alzheimer disease. Prog Brain Res 101: 383–390

Ventriglia M, Bocchio Chiavetto L, Benussi L, Binetti G, Zanetti O, Riva MA, Gennarelli M (2002) Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. Mol Psychiatry 7: 136–137

Weese-Mayer DE, Bolk S, Silvestri JM, Chakravarti A (2002) Idiopathic congenital central hypoventilation syndrome: evaluation of brain derived neurotrophic factor genomic DNA sequence variation. Am J Med Genet 107: 306–310

Wenham PR, Price WH, Blundell G (1991) Apolipoprotein E genotyping by one-stage PCR. Lancet 337: 1158–1159

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試案・提案

アルツハイマー病診断・評価基準試案

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要旨：日本人アルツハイマー病の遺伝的危険因子（感受性遺伝子）を全ゲノム解析によって同定するため，2000年に「脳科学の先端的研究」（略称「先端脳」；領域代表者：井原康夫）が開始された．「ヒトゲノム・遺伝子解析研究に関する倫理指針」を遵守し，各施設における倫理審査委員会の承諾のもとに本邦ではじめておこなわれている共同体（consortium）研究である．本研究では確実で均一なアルツハイマー病患者集団と正常対照者集団の遺伝子を対比して解析するために，従来のアルツハイマー病の診断や検査法の検討を元に診断評価基準試案を作成し，遺伝子を採取する医師，施設間で標準化をおこなった．この基準はアルツハイマー病の定義，DSM-IV，NINCDS-ADRDAおよびICD-10に準拠した診断基準，除外診断基準，必須およびより詳細な神経心理学的検査，必須および必要に応じた血液生化学的検査をふくむ広義の臨床診断基準と画像診断，生物学的マーカーおよび確定診断基準，臨床病型および類縁疾患からなっている．本試案をもとに，evidenceを有し，臨床的に広く使用される新たなアルツハイマー病の診断基準と評価法が本邦において確立されることが期待される．

（臨床神経，45：128—137，2005）
Key words：アルツハイマー病，診断・評価基準，先端脳，ゲノム班

はじめに

先進各国では人口の高齢化とともに痴呆患者が急増しており，痴呆疾患のケア・治療は医療的および社会経済的に早急に解決すべき重大な課題である．本邦における痴呆患者は現在170万人とされ，2025年には300万人に達すると推計されている．この多くを占めるのがアルツハイマー病（Alzheimer's disease）であり，米国における同患者数は現在400万人とされている．本邦でも同患者数はすでに100万人と推計され，脳血管障害とともにもっとも多い神経疾患である．アルツハイマー病は発症から3～8年のうちに半数の患者が死亡する[1)～3)]．一度発症すると持続的に進行し，確実に死亡にいたる予後不良の疾患である．したがって，多くの他の神経変性疾患と同様に，専門医による確実な診断がなされ，新たに発表された日本神経学会痴呆疾患治療ガイドライン2002[4)]に準拠した良質な医学的対処が望まれる．

現在，アルツハイマー病の原因解明のために，本邦および世界で最先端の研究がおこなわれている．この中で，日本人アルツハイマー病の遺伝的危険因子（感受性遺伝子）を全ゲノム解析によって同定するため，2000年に「脳科学の先端的研究」（略称「先端脳」；領域代表者：井原康夫）内にゲノム班が組織された．文部科学省，厚生労働省および経済産業省の3省合同による「ヒトゲノム・遺伝子解析研究に関する倫理指針」[5)]を遵守し，各施設における倫理審査委員会の承諾のもとに本邦ではじめておこなわれている共同体（consortium）研究である．到達目標として，日本人アルツハイマー病患者および正常対照者のそれぞれ2,000例と同胞発症200家系の遺伝子の採取とそのcase-control studyあるいは相関解析による日本人の遺伝的危険因子の同定をめざしている．本研究ではすでに55施設で協力がえられ，現在までに孤発例アルツハイマー病患者1,847例，正常対照者2,350例，同胞発症52家系106例の集積がおこなわれた．

本研究をさらに確実なものとするためには，医学的根拠（evidence）に基づいた診断と痴呆の評価法によって確実で均一なアルツハイマー病患者集団と正常対照者集団の遺伝子を対比して検討する必要がある．本研究班はこの目的のために，医師，地域，もちいた診断基準や痴呆の神経心理学的検査の種

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類による誤差をさけるため，欧米や本邦においてこれまで類用されてきたアルツハイマー病の診断基準，正常対照基準，神経心理学的検査を以下の5つの観点から再検討を加え，遺伝子を採取する医師，施設間で標準化を試みた．

1）国際的に広く使用されている診断基準や評価法であること．

2）すでに批判的査読（review）がおこなわれ，class Iないし class II の evidence を有すること．

3）感度（sensitivity）と特異性（specificity）が，prospective study をふくむ大規模多施設試験で確認・公表されていること．

4）神経心理学的検査は邦訳された日本語版があること．

5）神経心理学的検査の平均と標準偏差が各年齢別に日本人で標準化されており，とくに75歳以上でも有効な評価が可能であること．

しかしこの過程で，2001年の American Academy of Neurology Quality Standard Subcommittee の勧告[6]で指摘されたごとく，従来の診断基準の感度・特異性においても必ずしも十分な evidence がえられているわけではないこと，本邦では1995年に厚生省特定疾患研究，アミロイドーシス研究班によってアルツハイマー病の診断基準[7]が作成されたが一般的な使用にはいたらず，主に欧米の診断基準が使用されてきたこと，また，日本人における evidence の検討も不十分なことが判明した．さらに，発展しつつある画像診断や生物学的マーカーの研究成果が取り入れられていないこと，妥当とされる神経心理学的検査が少なく，臨床的にきわめて重要な75歳以上の高齢者における標準化がなされていないことなどが問題点として指摘された．

以上の経緯から，本研究班は evidence を有し，臨床的に広く使用されるアルツハイマー病の診断基準と評価法が本邦において新たに確立されるべきであると考えた．また，患者や家族にアルツハイマー病を告知し同意をえるには，このように標準化された診断・評価基準に基づくことが有用と思われる．本研究班はこのために，これまでわれわれが遺伝子採取時に標準化を行った診断基準と神経心理学的評価法の要旨を本誌に公表して，アルツハイマー病および関連痴呆疾患の診療を専門とする臨床医のこの問題に対する注意と議論を喚起することで意見が一致した（Table 1）．専門医の忌憚のないご意見とご批判をいただければ幸いである．

アルツハイマー病の定義

診断基準には最新の研究成果に基づいた疾患の正確な定義が必要と思われる．従来のアルツハイマー病の診断基準にこの項目はみられない．本診断基準では現在，もっとも広く consensus がえられているアルツハイマー病の脳病理変化に基づいて以下の定義をおこなった．「一度発達した知的機能が，脳への Aβ と tau の蓄積にともなって緩徐進行性に障害される疾患である」．

I-1．臨床診断基準（狭義）

我が国では従来，主にアメリカ精神医学会の診断基準（DSM-IV）[8] あるいは NINCDS-ADRDA work group の診断基準[9]に準拠してアルツハイマー病の臨床診断がおこなわれてきた．このうち，NINCDS-ADRDA work group の診断基準は記憶障害の進行観察期間を12カ月と改訂されて，1986年に The Consortium to Establish a Registry for Alzheimer's Disease（CERAD）の臨床診断基準として採用され[10]，剖検所見との対応など様々な検討がなされている．この2つの診断基準は，American Academy of Neurology Quality Standard Subcommittee による査読（review）では，3つの Class I 研究と10の Class II 研究があり，信頼性は0.95，感度は0.81（0.49～1.00），特異性は0.70（0.47～1.00）と評価され[11)~22)]，guideline として勧告された[6]．したがって，DSM-IV と NINCDS-ADRDA work group の診断基準は現時点で最高の診断感度と特異性を有し，国際的にも広く使用されていることから，われわれはこの2つの診断基準に準拠することが妥当と考えた．

両者の診断基準を比較すると各項目はきわめて類似しており，その要点は1）記憶障害が主要症状であること，2）失語，失行，失認の大脳皮質症状や物事を計画，組織化し，順序立てて遂行する実行機能障害があり，3）緩徐な発症と進行性の経過をとり，4）これらの症状によって発症以前にくらべて社会生活や日常生活の遂行が障害されていること，5）痴呆の原因としてアルツハイマー病以外の痴呆疾患が鑑別されていることに要約される．痴呆の診断は即断せずに，ある一定期間観察して，症状の進行を確認すべきであるとされている．この観察期間を明瞭に規定したものとして ICD-10 がある[23]．ICD-10 では痴呆の診断には少なくとも6カ月間の観察が必要との項目があり，本診断基準で採用した．

以上のことから，本診断基準では DSM-IV，NINCDS-ADRDA のアルツハイマー病の診断基準および ICD-10 痴呆の診断基準に準処し，とくに以下の要点を満たすことと規定した．

1）記憶障害がみられる．

2）失語，失行，失認，実行機能障害の少なくとも1つ以上がみられる．

3）緩徐な発症と症状が少なくとも6カ月間は持続的に進行する．

4）社会・日常生活機能のいちじるしい低下がみられる．

5）原因としてアルツハイマー病以外の痴呆疾患が否定できる．

これらの基準は必ずしも操作的ではないが，以下に選択された評価法によって客観的に示される必要がある．

I-2．除外診断基準

近年の研究の進歩はレビー小体型痴呆（Dementia with Lewy bodies：DLB）がアルツハイマー病に次いで多い痴呆性変性疾患であること，FTDP-17 の原因遺伝子が tau であることを明らかにして，前頭側頭型痴呆 Frontotemporal dementia（FTD）をはじめとして tauopathy と総称される様々な痴

Table 1　A proposal for diagnosis and clinical assessment criteria for Alzheimer's disease (Advanced Brain Science Project, The Japanese study group of genome-wide screening for genes associated with Alzheimer's disease)

Definition : A disorder in which once developed intellectual function is gradually and progressively impaired with Aβ and tau accumulation in the brain.

Ⅰ. Clinical diagnostic criteria (broad sense)
1. Clinical diagnostic criteria (narrow sense)
The diagnosis is based on the diagnostic criteria of Alzheimer's disease in DSM-Ⅳ and NINCDS-ADRDA and those of dementia in ICD-10, and particularly the following criteria should be fulfilled.
1) Presence of memory deficits
2) Presence of at least 1 of aphasia, apraxia, agnosia, and execution function deficits
3) Gradual onset and continuous progression of symptoms at least for 6 months
4) Marked decreases in social/daily living functions
5) As a cause, dementia disorders other than Alzheimer's disease can be excluded.
2. Exclusion diagnostic criteria
To exclude major dementia disorders other than Alzheimer's disease, the following diagnostic criteria are used as references.
1) Report of the NINDS-AIREN international workshop for Vascular dementia
2) Consensus guideline for clinical and pathologic diagnosis of dementia with Lewy bodies (DLB)
3) A consensus on clinical diagnostic criteria for frontotemporal dementia (FTD)
4) Clinical research criteria for the diagnosis of progressive supranuclear palsy by the NINDS-SPSP international workshop
3. Neuropsychological assessment
1) Indispensable examinations
Mini-Mental State Examination (MMS)
Functional Assessment Staging (FAST)
Clinical Dementia Rating (CDR)
2) More detailed examinations
Checklist for aphasia, apraxia, and agnosia (OHCL)
Troublesome behavior scale (TBS)
Wechsler Adult Intelligence Scale-Revised (WAIS-R)
Wechsler Memory Scale-Revised (WMS-R)
Alzheimer's Disease Assessment Scale, cognitive subscale, Japanese version (ADAS-Jcog)
4. Routine examinations
1) Indispensable items
Chest XP, ECG, EEG, blood cell counts, erythrocyte sedimentation rate, blood glucose, general biochemical examinations, and electrolytes (Na, K, Cl, Ca).
Renal function, ammonia, thyroid function, TPHA
2) Examinations performed when necessary
Blood gas, cerebrospinal fluid examination (properties, pressure, cell counts, protein, glucose, and IgG), and examination of VitB12, VitB1, folic acid, and nicotinic acid are performed. Examination of HIV antibody is performed with patient's consent.

Ⅱ. Imaging analysis
CT, MRI
Progression of bilateral atrophy in the hippocampus, medial surface of the temporal lobe, and the parietal lobe more positively supports the diagnosis. However, atrophy in other areas does not exclude this disease.
There are no lesions due to other disorders that can explain dementia.
SPECT, PET
A bilateral decrease in cerebral blood flow and metabolism in the hippocampus, medial surface of the temporal lobe, parietal lobe, and posterior cingulate gyrus can be demonstrated quantitatively or objectively by statistical processing using e-ZIS or 3D-SSP. The presence of a typical pattern supports the diagnosis of Alzheimer's disease, but the presence of a different pattern does not exclude this disease.

Ⅲ. Biological markers
An increase in tau or phosphorylated tau in cerebrospinal fluid is observed.
A decrease in Aβ42 or an increase in the Aβ40/42 is observed.

Ⅳ. Definite diagnostic criteria
Pathological criteria : CERAD pathologic criteria
Biochemical : Accumulation of ≥ 0.5 nmol/wet g brain Aβ40, 42 in the formic acid-extracted fraction
Sarkosyl-insoluble fraction showing a hyper-phosphorylated 3- and 4-repeat tau isoform accumulation pattern
Genetic diagnosis : Presence of mutant APP, mutant presenilin-1, -2, trisomy 21
Presence of mutant tau, or mutant prion can exclude Alzheimer's disease.
Risk factor : Apolipoprotein E ε4 allele

Ⅴ. Clinical types
Familial, sibling, sporadic
Early onset, late onset

Ⅵ. Related disorders
Dementia with Lewy bodies (common form), Down syndrome, cerebral amyloid angiopathy, dementia pugilistica

Ⅶ. Diagnosis of Alzheimer's disease
Definite AD : Ⅰ, Ⅱ, Ⅲ, Ⅳ
Probable AD : Ⅰ, Ⅱ (Examination of Ⅲ is desirable.)

呆性変性疾患の存在を明らかにしてきた．脳血管性痴呆（cerebrovascular dementia : VD），DLB，FTD および進行性核上性麻痺（Progressive supranuclear palsy : PSP）は頻度が高く，アルツハイマー病との鑑別にとくに注意を要する疾患である．これらの疾患にはすでに診断基準が提唱されており，いずれも診断感度は低いが，疾患特異性は高いと報告されている[6]．VD の診断基準である NINDS-AIREN 基準[24][25]では1つの Class Ⅰ研究があり，感度 0.43，特異性 0.95 であった[13]．DLB の診断基準[26]には1つの Class Ⅰ研究で感度 0.22，特異性 1.00，5つの Class Ⅱ研究で平均感度 0.58（0.34～0.75），特異性 0.87（0.71～0.94）であった[6][27][28]．FTD の診断基準[29]では感度 0.63～0.73，特異性 0.97～1.00 と報告された．PSP の診断基準[30][31]は感度 0.5～0.75，特異性 0.99 と報告されている．本診断基準ではこれらの頻度の高いアルツハイマー病以外の痴呆疾患の除外のため，以下の4つの基準を除外診断基準として採用した．

1．Report of the NINDS-AIREN international workshop for Vascular dementia[24]

2．Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies（DLB）[26]

3．A consensus on clinical diagnostic criteria for frontotemporal dementia（FTD）[29]

4．Clinical research criteria for the diagnosis of progressive supranuclear palsy by the NINDS-SPSP international workshop[30]

I-3．神経心理学的評価

1）必須検査

長谷川式簡易知能評価スケール改訂版（HDS-R）[32]および Mini-Mental State Examination（MMS）[33]は本邦でもっとも広汎に使用されている痴呆のスクリーニングスケールである．HDS-R はカットオフ値を 20/21 点と設定すると痴呆の鑑別は感度 0.90，特異性 0.82 で，年齢や教育年数との相関はなく，評価間信頼性は 0.90，MMS との相関は 0.94 である[32]．MMS は世界中の臨床論文で頻用され，塩酸ドネペジルの臨床試験にも使用され，世界各国で共通の痴呆スクリーニングスケールとなりつつある．検査の評価者間再現性は 0.83～

Table 2　Aphasia/apraxia/agnosia checklist (OHCL)

		Dominant hand (right	left)	
1. Verbal fluency, speech, understanding, repetition	Aphasia	+	−	(MMS)
2. Can not read/write	Alexia/agraphia	+	−	(MMS)
3. Subtract 7 by 7 from 100.	Acalculia	+	−	(MMS)
4. Walk.	Gait apraxia	+	−	
5. Frown, whistle.	Facial apraxia	+	−	
6. Touch the other fingers with the thumb in the order of their arrangement.	Limb-kinetic apraxia	+	−	
Pick at objects, fasten buttons.	(Poor motions of the upper and lower limbs)	+	−	
Form a fox, pistol, and scissors using the fingers				
7. Make tooth-brushing and hair-brushing gestures.	Ideomotor apraxia	+	−	
Wave a hand, beckon.	(Impaired imitation of actions and use of objects)	+	−	
8. Do (6) and (7) using the left hand.	Left side apraxia	+	−	
9. Light a cigarette with a match.	Ideational apraxia	+	−	
Make tea using a tea canister, teapot, and thermos.	(Disorder in use of daily necessities)	+	−	
10. Dress	Dressing apraxia	+	−	
11. Draw a cube and pentagons overlapping with each other.	Constructional apraxia	+	−	(MMS)
Draw a clock.				(clock drow)
12. Draw a human face.	hemi-spatial agnosia	+	−	
Mark the center of the line.				
13. What is this?	Visual agnosia	+	−	
14. What color is this?	Color agnosia	+	−	
15. Which face shows weeping?	Prosopagnosia	+	−	
Who is this person?				
16. What is there in this?	Visual-spatial agnosia	+	−	
17. Have you ever been lost?	Topographical disorientation	+	−	
18. Which is your eye, mouth, or nose?	Asomatognosia	+	−	
19. Which is your left hand/right ear?	Right-left agnosia	+	−	
20. Which is your thumb/ring finger?	Finger agnosia	+	−	
21. What trouble do you have?	Anosognosia	+	−	
22. What is this? (After the patient touches an object with the eyes closed.)	Tactile agnosia	+	−	

Notes : The examination can be discontinued when 2 or more +s are found.
Other comments :

☐ saving appearance ☐ looking back ☐ twilight syndrome ☐ closing-in phenomenon ☐ disinhibition ☐ mirror phenomenon
☐ Capgra syndrome ☐ phantom boarder ☐ Bálint syndrome

0.98 で[33]，2つの Class I study で感度 0.49～0.63，特異性 0.92～0.96 であった[34]．日本語版[35]でカットオフ値を 23/24 点と設定した検討では，感度 0.83～0.92，特異性 0.92～0.93 であり，HDS-R と同様に高い値を示している．WAIS との相関は 0.84，試験間の再現性は 0.91 であった[35][36]．75 歳以上の高齢者の検討や教育の影響などが報告されており[37][38]，NINCDS-ADRDA 診断基準の 1 項目となっているため[10]，本診断基準では MMS の使用を採択した．

痴呆の重症度分類としての Functional Assessment Staging (FAST) はアルツハイマー病の日常生活機能を障害程度によって分類したものである[39]．正常老化をふくめ全部で 7 段階に病期が分類され，進行の自然経過と予後が具体的に記述してある．アルツハイマー病の重症度分類としてよく使用されており，新たな薬剤の臨床治験にも頻用されている．評価者間信頼性は 0.59～0.87 で，MMS との相関は 0.79～0.87 である[40][41]．Clinical Dementia Rating (CDR) は最近よく使用されている痴呆の重症度評価基準[42]～[44]で，CERAD で使用され[45]，軽度認知障害 (mild cognitive impairment : MCI) の診断根拠の 1 項目となっている[46][47]．評価者間信頼性は 0.89 で，CDR 0 は FAST 1～2，CDR 0.5 は FAST 3～4，CDR 1 は FAST 5，CDR 2 は FAST 6，CDR 3 は FAST 6～7 に相当する[41]．

CDR は世界各国の臨床論文で頻用される共通の痴呆重症度スケールとなりつつあり，国際的に発表するばあいは必須と考えられる．また，CDR 1 以上をもちいれば，MCI を除外できる可能性がある．しかし，CDR のそれぞれの下位項目は曖昧で，家族からの聞き取りのみでは評者間で相違する可能性が懸念される．FAST はアルツハイマー病の重症度を具体的に記述してあるため，家族からの聞き取りでも，ほぼ均一な結果をえることが可能で，CDR との相関も発表されている[41]．以上のことから，聞き取りにともなう曖昧さを回避するために，本基準ではアルツハイマー病の重症度の評価は CDR と FAST の両者を必須の検査として採択した．

2) より詳細な検査

失語，失行，失認などの大脳皮質症状の存在をもれなく客観的に評価する必要がある．本邦では失語症の評価には標準失

語症検査（standard language test of aphasia：SLTA）[48]やWAB失語症検査日本語版[49]などが使用されているが，失行や失認の標準化された試験は現在準備段階である（標準高次動作性検査）[50]．外来診療の短時間にこれらの症状を簡単にスクリーニングするためには，まとまったチェックリストが有用である．このような目的のために現在公開されているのは岡山大学附属病院神経内科で使用されている失語，失行，失認チェックリスト[51]のみであるため，このチェックリストをもとにアルツハイマー病で頻度の高い症状を追加して，高次機能チェックリストとして新たに作成した（Okayama Higher Cortical Function check list：OHCL，Table 2）．同様に，アルツハイマー病の周辺症状としての問題行動を評価することも重要である．この目的のために作成された基準のうち，朝田らの問題行動評価尺度（troublesome behavior scale：TBS）[52]が試験および評価者間の信頼性が本邦で検討されている．異常行動と精神症状にはBehave-AD[53][54]が，精神症状の評価にはNeuropsychaitry Inventory（NPI）[55][56]もよく使用されている．両者とも本邦の患者で信頼性が検討されている．本評価基準ではより簡便で具体的な問題行動のみを評価できるTBSを採用した．

Wechsler Adult Intelligence Scale-Revised（WAIS-R）[57]は世界でもっとも普及している知能評価スケールであり，邦訳された日本語版がこの目的のために使用されている．言語性，動作性の両者のIQが正確に決定できるが，検査に時間がかかりルーチン検査に向いていない．痴呆患者では検査の実施そのものが困難な例もみられる．また，評価年齢範囲が16～74歳であり，75歳以上では標準化された情報がないため，高齢のアルツハイマー病患者では曖昧な結果が懸念される．本邦では日常診察するアルツハイマー病患者が75歳以上の高齢者となりつつあるため，75歳以上の高齢者におけるWAIS-R検査結果の年齢階層別の標準化が早急に望まれる．

Wechsler Memory Scale-Revised（WMS-R）は2001年に杉下らによって日本語版が作成され，日本人で標準化がなされた[58]．記憶記銘障害を正確に評価できる唯一の検査スケールであるが，WAIS-Rと同様に検査に時間がかかり，75歳以上では標準化がなされていない．本邦でおこなわれた検討ではアルツハイマー病で感度0.93，特異性0.92であった[59]．Alzheimer's Disease Assessment Scale（ADAS）は1983年にMohsらによって開発され，記憶を中心とする認知機能検査ADAS-cognitive subscale（ADAS-cog）と非認知機能検査ADAS-non cognitive subscale（ADAS-non cog）からなり，塩酸ドネペジルなどの薬物による認知機能変化の評価を主な目的としており，多くの臨床治験で使用されている[60][61]．日本版（ADAS-Jcog）[62]は本間らによって1992年に作成され，痴呆群ではADAS-Jcog得点間に相関はなく，再検査による信頼性ではアルツハイマー病患者群，正常対照者群ではそれぞれ0.95，0.82で，十分な信頼性がえられている．FAST，MMS得点との相関は0.72，−0.81である．山下らは9/10点をカットオフ値とすると認知障害の有無を感度0.98，特異性0.95で判定できるとしている[63]．

これらのより詳細な検査は必要に応じて使用する．WAIS-R，WMS-RとADAS-Jcogは複雑で施行により長時間かかるため，習熟した臨床心理士がおこない，結果を記載することが望ましい．

I-4．一般検査

1）外来時一般検査として，胸部XP，ECG，EEG，血算，血沈，血糖，一般生化学検査，電解質（Na，K，Cl，Ca），腎機能，アンモニア，甲状腺機能，TPHAを必須検査としておこなう必要がある．

2）血液ガス，脳脊髄液検査（性状，圧，細胞数，蛋白，糖，IgG），VitB12，VitB1，葉酸およびニコチン酸などの検査を必要に応じておこなう．HIV抗体は患者の同意があればおこなう．

II．画像診断

画像診断はアルツハイマー病と他の痴呆疾患との鑑別にきわめて重要な検査であるにもかかわらず，これまでアルツハイマー病を積極的に示唆する画像所見をふくむ診断基準は一般化していない．また，prospective studyによる感度と特異性，剖検所見との対応によるevidenceの検討も不十分である[6]．それぞれの検査のEvidence based studyによる検討が今後の課題である．本診断基準ではCT，MRI所見として，海馬，側頭葉内側面，頭頂葉で両側性に萎縮が進行することを重視した．また，痴呆を説明する他の疾患による病巣がみられないことも必要である．SPECT，PETでは3D-SSP[64]やe-ZIS[65]などの新たな統計処理画像が一般の病院でも可能となり，より客観的な判断が可能となりつつある．本診断基準では海馬，側頭葉内側面，頭頂葉の両側性脳血流代謝の低下，初期では後部帯状回における血流低下の定量的客観的な証明が必要である．アルツハイマー病では非典型的な部位の萎縮を示す例が時に存在するため，CTやMRIによる非典型的な部位の萎縮やSPECT，PETでことなる障害パターンがみられても，アルツハイマー病を否定することは妥当ではない．

III．生物学的マーカー

ここ数年の間に本邦を中心として脳脊髄液（CSF）マーカーの重要性が報告されてきた．現在までにAβは17施設，tauは34の施設で多施設共同研究として検討された[66]～[69]．2003年にはSunderlandらによってMeta-analysisがおこなわれた[70]．最近のBlennowらの総説では[71]，両者を使用すると診断感度，特異性ともに80%を超しており，prospective studyや病理所見との対応も報告された[72][73]．Down症候群やMCIでも検討され，早期診断における有用性も指摘されている．Aβやtauでは加齢による生理的変化や多くの中枢神経疾患における測定結果などの基本的情報も集積している[67][68]．したがって，CSF Aβ40，Aβ42およびtauは可能なかぎり測定すべき項目と考えられる．

CSFリン酸化tauはアルツハイマー病により特異性を有するマーカーと期待されているが，total tauにくらべて，多施設共同研究成果をはじめとする基礎的情報が未だに乏しく，どのtauリン酸化部位の測定が有用であるかの検討も不十分であるため[74][75]，今後の発展が期待される．

IV．確定診断基準

確定診断としては現在も病理学的検索が必要である．病理学的診断基準として一般的なものとしてCERAD[76]，Braakらによる Stage 分類[77]などがある．このうち，CERAD の病理診断基準は鍍銀染色で染色した典型的老人斑の数を半定量するもので，アルツハイマー病の病理変化がもっとも激しい新皮質において 2/mm² を sparse，6/mm² を moderate，35/mm² を frequent に分類し，年齢階層別に標準化した老人斑数と比較して，definite，probable，possible，normal と評価するものである．臨床診断基準である改訂 NINCDS-ADRDA 診断基準による probable AD と CERAD アルツハイマー病病理診断基準 definite との一致率は 84～87%であった[76][78][79]．神経原線維変化の評価などに問題点を有するが，現時点では以上に述べた多数例での臨床と病理の対応が検討されていることから，CERAD 診断基準の採用が適当と考えた．

最近の研究ではアルツハイマー病患者脳では組織学的に典型的老人斑や神経原線維変化の出現する前に，すでに生化学的レベルでは Aβ，tau ともに多量に蓄積しており，行動障害とも密接に関連することがモデル動物レベルの研究で示されている．したがって，本診断基準では生化学的基準の項を設け，蟻酸抽出分画における Aβ40，Aβ42 の 0.5nmol/wet g brain 以上の蓄積[80]および Sarkosyl 不溶性分画における過剰にリン酸化した 3 および 4 repeat tau の蓄積パターンの存在[81]を加えた．

遺伝子レベルでは，変異 amyloid β protein precursor (βAPP)，変異 presenilin-1，-2，trisomy 21 などの既知の家族性アルツハイマー病遺伝子異常が判明したばあいは，家族性アルツハイマー病あるいは Down 症候群と確定診断可能である[82]．他疾患の除外には変異 tau 遺伝子が判明したばあいは FTDP-17，変異 prion が判明すれば，家族性プリオン病[83]として確定診断可能である．Apolipoprotein ε4 allele が最強のアルツハイマー病危険因子遺伝子として明らかにされている[84]．患者の同意があったばあい，Apolipoprotein ε4 allele を検討し，併記すべきである．

V．臨床病型

本研究では孤発性アルツハイマー病，同胞発症 (sibling) のアルツハイマー病の遺伝子を採取し，全ゲノム解析をおこなうため，家族性，同胞発症 (affected sib-pair)，孤発性に分類し，従来の分類と同様に 65 歳未満発症を早期発症，それよりも高齢発症を晩期発症と分類する．

VI．類縁疾患

脳に Aβ と tau の蓄積がみられる DLB (common form)，Down syndrome，Cerebral amyloid angiopathy，Dementia pugilistica を類縁疾患として分類した．

VII．アルツハイマー病の診断

以上に述べたアルツハイマー病の診断・評価基準試案のうち I，II，III および IV を満たすものを Definite AD とする．Probable AD として I および II を満たすものとする．III は実施することが望ましい．

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文　献

1) Helmer C, Joly P, Letenneur L, et al : Mortality with dementia : results from a French prospective community-based cohort. Am J Epidemiol 2001 ; 154 : 642—648
2) Brookmeyer R, Corrada MM, Curriero FC, et al : Survival following a diagnosis of Alzheimer disease. Arch Neurol 2002 ; 59 : 1764—1767
3) Wolfson C, Wolfson DB, Asgharian M, et al : Clinical Progression of Dementia Study Group : A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001 ; 344 : 1111—1116
4) 痴呆疾患治療ガイドライン作成小委員会：痴呆疾患治療ガイドライン 2002. 臨床神経　2002 ; 42 : 788—832
5) 文部科学省・厚生労働省・経済産業省：ヒトゲノム・遺伝子解析研究に関する倫理指針，告示第一号，2000
6) Knopman DS, DeKosky ST, Cummings JL, et al : Practice parameter : diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001 ; 56 : 1143—1153
7) 石原得博：アミロイドーシスの診断基準．厚生省特定疾患研究，アミロイドーシス調査研究班．1995 年度研究報告書，1996, pp 13—23
8) American Psychiatric Association : Diagnostic and statistical manual of mental disorders 4th edition, American Psychiatric Association, Washington DC, 1994
9) McKhann G, Drachman D, Folstein M, et al : 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
10) Morris JC, Heyman A, Mohs RC, et al : The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989 ; 39 : 1159—1165
11) Blacker D, Albert MS, Bassett SS, et al : Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. The National Institute of Mental Health Genetics Initiative. Arch Neurol 1994 ; 51 : 1198—1204
12) Forette F, Henry JF, Orgogozo JM, et al : Reliability of clinical criteria for the diagnosis of dementia. A longitudinal multicenter study. Arch Neurol 1989 ; 46 : 646—648
13) Holmes C, Cairns N, Lantos P, et al : Validity of current clinical criteria for Alzheimer's disease, vascular dementia and dementia with Lewy bodies. Br J Psychiatry 1999 ; 174 : 45—50
14) Jobst KA, Barnetson LP, Shepstone BJ : Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia : the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and apo E4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging. Int Psychogeriatr 1998 ; 10 : 271—302
15) Lim A, Tsuang D, Kukull W, et al : Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. J Am Geriatr Soc 1999 ; 47 : 564—569
16) Wade JP, Mirsen TR, Hachinski VC, et al : The clinical diagnosis of Alzheimer's disease. Arch Neurol 1987 ; 44 : 24—29
17) Victoroff J, Mack WJ, Lyness SA, et al : Multicenter clinicopathological correlation in dementia. Am J Psychiatry 1995 ; 152 : 1476—1484
18) Galasko D, Hansen LA, Katzman R, et al : Clinical-neuropathological correlations in Alzheimer's disease and related dementias. Arch Neurol 1994 ; 51 : 888—895
19) Mayeux R, Saunders AM, Shea S, et al : Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med 1998 ; 338 : 506—511
20) Klatka LA, Schiffer RB, Powers JM, et al : Incorrect diagnosis of Alzheimer's disease. A clinicopathologic study. Arch Neurol 1997 ; 53 : 35—42
21) Berg L, McKeel DW Jr., Miller JP, et al : Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease : relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 1998 ; 55 : 326—335
22) Massoud F, Devi G, Stern Y, et al : A clinicopathological comparison of community-based and clinic-based cohorts of patients with dementia. Arch Neurol 1999 ; 56 : 1368—1373
23) World Health Organization : The ICD-10 classification of mental and behavioral disorders ; Clinical Descriptions and diagnostic guidelines. WHO, Geneva, 1992
24) Roman GC, Tatemichi TK, Erkinjuntti T, et al : Vascular dementia : diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993 ; 43 : 250—260
25) Gold G, Giannakopoulos P, Montes-Paixao Junior C, et al : Sensitivity and specificity of newly proposed clinical criteria for possible vascular dementia. Neurology 1997 ; 49 : 690—694
26) McKeith IG, Galasko D, Kosaka K, et al : Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB) : report of the consortium on DLB international workshop. Neurology 1996 ; 47 : 1113—1124

27) McKeith IG, Perry EK, Perry RH : Report of the second dementia with Lewy body international workshop : diagnosis and treatment. Consortium on Dementia with Lewy Bodies. Neurology 1999 ; 53 : 902—905
28) Litvan I, MacIntyre A, Goetz CG, et al : Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies : a clinicopathologic study. Arch Neurol 1998 ; 55 : 969—978
29) Neary D, Snowden JS, Gustafson L, et al : Frontotemporal lobar degeneration : a consensus on clinical diagnostic criteria. Neurology 1998 ; 51 : 1546—1554
30) Litvan I, Agid Y, Calne D, et al : 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
31) Lopez OL, Litvan I, Catt KE, et al : Accuracy of four clinical diagnostic criteria for the diagnosis of neurodegenerative dementias. Neurology 1999 ; 53 : 1292—1299
32) 加藤伸司，長谷川和夫，下垣　光ら：改訂長谷川式簡易知能評価スケール（HDS-R）の作成．老年精神医学雑誌 1991 ; 2 : 1339—1347
33) 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
34) Petersen RC, Stevens JC, Ganguli M, et al : Practice parameter : early detection of dementia : mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001 ; 56 : 1133—1142
35) 森　悦朗，三谷洋子，山鳥　重：神経疾患患者における日本語版 Mimi-mental State テストの有用性．神経心理学 1985 ; 1 : 82—90
36) 川畑信也，横山さくら，彦坂しのぶら：Mini-Mental State Examination（MMSE），痴呆症学　1. 日本臨床　2004 ; 61（増刊号 9）: 192—197
37) Dufouil C, Clayton D, Brayne C, et al : Population norms for the MMSE in the very old : estimates based on longitudinal data. Mini-Mental State Examination. Neurology 2000 ; 55 : 1609—1613
38) Crum RM, Anthony JC, Bassett SS, et al : Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993 ; 269 : 2386—2391
39) Reisberg B Ferris SH, Anand R, et al : Functional staging of dementia of the Alzheimer's type. Ann NY Acad Sci 1984 ; 435 : 481—483
40) Sclan SG, Reisberg B : Functional assessment staging (FAST) in Alzheimer's disease : reliability, validity, and ordinality. Int Psychogeriatr 1992 ; 4 Suppl 1 : 55—69
41) 本間　昭，臼井樹子：Functional Assessment Staging (FAST)，痴呆症学 1. 日本臨床　2004 ; 61（増刊号 9）: 125—128
42) Hughes CP, Berg L, Danziger WL, et al : A new clinical scale for the staging of dementia. Br J Psychiat 1982 ; 140 : 566—572
43) Morris JC : The Clinical Dementia Rating (CDR) : current version and scoring rules. Neurology 1993 ; 43 : 2412—2414
44) Burke WJ, Miller JP, Rubin EH, et al : Reliability of the Washington University Clinical Dementia Rating. Arch Neurol 1988 ; 45 : 31—32
45) Tariot PN, Mack JL, Patterson MB, et al : The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. Am J Psychiatry 1995 ; 152 : 1349—1357
46) Morris JC, Storandt M, Miller JP, et al : Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001 ; 58 : 397—405
47) Petersen RC, Smith GE, Waring SC, et al : Mild cognitive impairment : clinical characterization and outcome. Arch Neurol 1999 ; 56 : 303—308
48) 標準失語症検査制作委員会：標準失語症検査，鳳鳴道書店，1975，改訂版，新興医学出版社，東京，1997
49) WAB 失語症検査（日本語版）作成委員会：WAB 失語症検査．日本語版，医学書院，東京，1986
50) 日本失語症学会高次動作性検査法制作小委員会：改訂版標準高次動作性検査—失行症を中心として．新興医学出版社，東京，1999
51) 阿部康二：神経内科　検査・処置マニュアル．新興医学出版社，東京，2001, p 207
52) 朝田　隆，吉岡　充，森川三郎ら：痴呆患者の問題行動評価表（TBS）の作成．日本公衆衛生雑誌　1994 ; 41 : 518—527
53) Reisberg B, Borenstein J, Salob SP, et al : Behavioral symptoms in Alzheimer's disease : phenomenology and treatment. J Clin Psychiatry 1987 ; 48 Suppl : 9—15
54) 朝田　隆，本間　昭，木村通宏ら：日本語版 BehaveAD の信頼性について．老年精神医学　1999 ; 10 : 825—834
55) Cummings JL, Mega M, Gray K, et al : The Neuropsychiatric Inventory : comprehensive assessment of psychopathology in dementia. Neurology 1994 ; 44 : 2308—2314
56) 博野伸次，森　悦朗，池尻義隆ら：日本語版 Neuropsychiatry Inventory—痴呆の精神症状評価法の有用性の検討．脳と神経　1997 ; 49 : 266—271
57) 品川不二郎，小林重雄，藤田和弘ら：日本版 WAIS-R 成人知能検査法．日本文化科学社，東京，1990

58) Wechsler D（著），杉下守弘（訳著）：日本語版ウエクスラー記憶検査法(WMS-R)，日本文化科学社，東京，2001
59) 新見裕之，博野信次，数井裕光ら：アルツハイマー型痴呆におけるウエクスラー記憶検査法修正版の有用性について．神経心理学　1999；17：43
60) Mohs RC, Rosen WG, Davis KL：The Alzheimer's disease assessment scale：an instrument for assessing treatment efficacy. Psychopharmacol Bull 1983；19：448—450
61) Rosen WG, Mohs RC, Davis KL：A new rating scale for Alzheimer's disease. Am J Psychiatry 1984；141：1356—1364
62) 本間　昭，福沢一吉，塚田良雄ら：Mhos RC：Alzheimer's Disease Assessment Scale（ADAS）日本語版の作成．老年神経医学雑誌　1992；3：645—655
63) 山下　光，博野伸次，池尻義隆ら：Alzheimer's disease Assessment Scale 日本語版（ADAS-Jcog）の有用性の検討．老年精神医学雑誌　1998；9：187—194
64) Minoshima S, Giordani B, Berent S, et al：Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997；42：85—94
65) Matsuda H, Ohnishi T, Asada T, et al：Correction for partial-volume effects on brain perfusion SPECT in healthy men. J Nucl Med 2003；44：1243—1252
66) Arai H, Terajima M, Miura M, et al：Tau in cerebrospinal fluid：a potential diagnostic marker in Alzheimer's disease. Ann Neurol 1995；38：649—652
67) Kanai M, Matsubara E, Isoe K, et al：Longitudinal study of cerebrospinal fluid levels of tau, A beta1-40, and Abeta 1-42（43）in Alzheimer's disease：a study in Japan. Ann Neurol 1998：44：17—26
68) Shoji M, Matsubara E, Murakami T, et al：Cerebrospinal fluid tau in dementia disorders：a large scale multicenter study by a Japanese study group. Neurobiol Aging 2002；23：363—370
69) Shoji M, Kanai M, Matsubara E, et al：Taps to Alzheimer's patients：a continuous Japanese study of cerebrospinal fluid biomarkers. Ann Neurol 2000；48：402
70) Sunderland T, Linker G, Mirza N, et al：Decreased beta-amyloid 1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. JAMA 2003；289：2094—2103
71) Blennow K, Hampel H：CSF markers for incipient Alzheimer's disease. Lancet Neurol 2003；2：605—613
72) Andreasen N, Minthon L, Davidsson P, et al：Evaluation of CSF-tau and CSF-Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. Arch Neurol 2001；58：373—379
73) Clark CM, Xie S, Chittams J, et al：Cerebrospinal fluid tau and beta-amyloid：how well do these biomarkers reflect autopsy-confirmed dementia diagnoses? Arch Neurol 2003；60：1696—1702
74) Itoh N, Arai H, Urakami K, et al：Large-scale, multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the antemortem diagnosis of Alzheimer's disease. Ann Neurol 2001；50：150—156
75) Hampel H, Buerger K, Zinkowski R, et al：Measurement of Phosphorylated Tau Epitopes in the Differential Diagnosis of Alzheimer Disease：A Comparative Cerebrospinal Fluid Study. Arch Gen Psychiatry 2004；61：95—102
76) Mirra SS, Heyman A, McKeel D, et al：The Consortium to Establish a Registry for Alzheimer's Disease（CERAD）. Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991；41：479—486
77) Braak H, Braak E：Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol（Berl）1991；82：239—259
78) Tierney MC, Fisher RH, Lewis AJ, et al：The NINCDS-ADRDA Work Group criteria for the clinical diagnosis of probable Alzheimer's disease：a clinicopathologic study of 57 cases. Neurology 1988；38：359—364
79) Gearing M, Mirra SS, Hedreen JC, et al：The Consortium to Establish a Registry for Alzheimer's Disease（CERAD）. Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. Neurology 1995；45（3 Pt 1）：461—466
80) Funato H, Yoshimura M, Kusui K, et al：Quantitation of amyloid beta-protein（A beta）in the cortex during aging and in Alzheimer's disease. Am J Pathol 1998；152：1633—1640
81) Spillantini MG, Goedert M：Tau protein pathology in neurodegenerative diseases. Trends Neurosci 1998；21：428—433
82) St George-Hyslop PH：Molecular genetics of Alzheimer's disease. Biol Psychiatry 2000；47：183—199
83) Hsiao K, Baker HF, Crow TJ, et al：Linkage of a prion protein missense variant to Gerstmann-Sträussler syndrome. Nature 1989；338：342—345
84) Corder EH, Saunders AM, Strittmatter WJ, et al：Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993；261：921—923

Abstract

A proposal for diagnostic and clinical assessment criteria for Alzheimer's disease

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To clarify the risk and associated genes of Alzheimer's disease by genome-wide screening, a Japanese study group was organized in 2000 under Yasuo Ihara, Tokyo University, supported by a Grant-in-Aid for Science Research on Priority Areas (C)-Advanced Brain Science Project from Ministry of Education, Culture, Sports, Science and Technology, Japan. This is the first Japanese consortium study under permission of the ethical committees of the enrolled institutes based on the ethics guidelines for human genome/gene analysis research, Ministry of Education, Culture, Sports, Science and Technology Ministry of Health, Labor and Welfare Ministry of Economy, Trade and Industry. In this project, 2,000 genome samples from patients with Alzheimer's disease, 2,000 control subjects, and 200 siblings affected with Alzheimer's disease are collected and analyzed. For this purpose, it is necessary to analyze samples from accurately diagnosed Alzheimer patients and controls using standard criteria for diagnosis and neuropsychological evaluation, which have been confirmed by an evidence-based studying a Japanese population. Here, we propose criteria for the diagnosis and clinical assessment of Alzheimer's disease. This proposal consists of a definition of Alzheimer's disease based on recent advances in research, diagnostic criteria based on DSM-IV, NINCDS-ADRDA and ICD-10, exclusion criteria for other dementia disorders, routine and detailed tests for neuropsychological and laboratory evaluations, criteria for neuroimaging and biomarkers, definitive diagnostic criteria and classification of clinical subtypes.

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Key words: Alzheimer's disease, diagnosis and clinical assessment, Advanced Brain Science Project, genome-wide screening by the Japanese study group

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Cognitive function in Japanese elderly with type 2 diabetes mellitus

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Abstract

The current study was conducted to investigate the cognitive function in Japanese elderly with type 2 diabetes mellitus (DM). Participants included 69 diabetic and 27 nondiabetic subjects (60 to 85 years old). The cognitive functional tests conducted were the Mini-Mental State Examination (MMSE), Word Lists Recall (immediate, delayed), Digit Symbol Test (Wechsler Adult Intelligence Scale—Revised [WAIS-R]), and the Stroop Color Word Test. Hemoglobin A1c (HbA1c) was measured as the index of glycemic control, and information about recent hypoglycemic episodes was gathered by using questionnaires. Student's *t* test showed that DM subjects had significantly lower scores in the MMSE ($P<.01$) and Digit Symbol Test ($P<.05$) than non-DM subjects. The scores of the Digit Symbol Test in diabetes subjects had a significant negative relationship with HbA1c ($r=-.433$; $P<.001$), and insulin-use had a significant relationship with the scores of the MMSE and Digit Symbol Test. Subjects in the DM group were further divided by insulin use. Comparison of insulin-treated DM subjects, non-insulin-treated DM subjects, and nondiabetic subjects by analysis of variance followed by Bonferroni's post hoc test showed that insulin-treated DM subjects had significantly lower scores in the MMSE and Digit Symbol Tests than both non-insulin-treated DM subjects ($P<.05$) and nondiabetic subjects ($P<.01$). Our study suggests that Japanese elderly DM subjects, especially those with insulin treatment, have poor cognitive function.

Keywords: Digit Symbol Test; MMSE; HbA1c; Insulin; Hypoglycemia

1. Introduction

Cognitive function in elderly diabetes mellitus (DM) subjects has been of interest for more than 80 years and has been explored in several studies; however, the outcomes of these studies have not been entirely conclusive (Strachan, Deary, Ewing, & Frier, 1997). Although most studies have concluded that cognitive performance is worse in elderly DM subjects (Gradman, Laws, Thompson, & Reaven, 1993; Miles & Root, 1922; Perlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990), some studies have reported that cognitive function in type 2 DM subjects is comparable to that in non-DM subjects (Atiea, Moses, & Sinclair, 1995; Mattlar, Falck, Ronnemaa, & Hyyppa, 1985). These studies have been performed mainly in Western countries. Because cognitive functional tests are based on language communication, studies should be performed using subjects with different genetic and cultural backgrounds in different languages.

Among the factors involved in the mechanism of cognitive impairment in DM subjects, glycemic control may be one of the most important (Gradman et al., 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993). Few studies have investigated the relationship between glycemic control and cognitive function in DM patients. However, one study reported that glycemic control, as measured by hemoglobin A1c (HbA1c) levels, showed a significant negative correlation with cognitive function in DM patients (Reaven et al., 1990). Another reported that oral hypoglycemic medication improved some domains of cognitive ability (attention/concentration, new learning, and problem solving) (Gradman

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classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine, 15*, 539–553.

Berkus, M.D, & Langer, O. (1993). Glucose tolerance test: degree of glucose abnormality correlates with neonatal outcome. *Obstetrics and Gynecology, 81*, 344–348.

Bonomo, M., Gandini, M. L., Farina, A., Bonfadini, E., Pisoni, M. P., Prudenziati, A., Mion, E., & Greco, P. (1997). Should we treat minor degrees of glucose intolerance in pregnancy? *Annalli dell'Istituto Superiore de Sanita, 33*, 393–397.

Brunskill, A. J., Rossing, M. A., Connell, E. A., & Daling, J. (1991). Antecedents of macrosomia. *Paediatric and Perinatal Epidemiology, 5*, 392–401.

Catalano, P. M., Roman, N. M., Tyzbir, E. D., Merritt, A. O., Driscoll, P., & Amini, S. B. (1993). Weight gain in women with gestational diabetes. *Obstetrics and Gynecology, 81*, 523–528.

Caulfield, L. E., Harris, S. B., Whalen, E. A., & Sugamori, M. E. (1998). Maternal nutritional status, diabetes and risk of macrosomia among Native Canadian women. *Early Human Development, 50*, 293–303.

Cundy, T., Gamble, G., Manuel, A., Townend, K., & Roberts, A. (1993). Determinants of birth-weight in women with established and gestational diabetes. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 33*, 249–254.

Di Cianni, G., Benzi, L., Bottone, P., Volpe, L., Orsini, P., Murru, S., Casadidio, I., Clemente, F., & Navalesi, R. (1996). Neonatal outcome and obstetric complications in women with gestational diabetes: effects of maternal body mass index. *International Journal of Obesity and Related Metabolic Disorder, 20*, 445–449.

Essel, J. K., & Opal-Tetteh, E. T. (1995). Macrosomia — maternal and fetal risk factors. *South African Medical Journal, 85*, 43–46.

Forsbach, G., Contreras-Soto, J. J., Fong, G., Flores, G., & Moreno, O. (1988). Prevalence of gestational diabetes and macrosomic newborns in a Mexican population. *Diabetes Care, 11*, 235–238.

Garner, P., Okun, N., Keely, E., Wells, G., Perkins, S., Sylvain, J., & Belcher, J. (1997). A randomized controlled trial of strict glycemic control and tertiary level obstetric care versus routine obstetric care in the management of gestational diabetes: a pilot study. *American Journal of Obstetrics and Gynecology, 177*, 190–195.

Green, J. R., Schumacher, L. B., Pawson, I. G., Partridge, J. C., & Kretchmer, N. (1991). Influence of maternal body habitus and glucose tolerance on birth weight. *Obstetrics and Gynecology, 78*, 235–240.

Hardy, D. S. (1999). A multiethnic study of the predictors of macrosomia. *Diabetes Educator, 25*, 925–933.

Khan, K. S., Syed, A. H., Hashmi, F. A., & Rizvi, J. H. (1994). Relationship of fetal macrosomia to a 75 g glucose challenge test in nondiabetic pregnant women. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 34*, 24–27.

Kieffer, E. C., Nolan, G. H., Carman, W. J., Sanborn, C. Z., Guzman, R., & Ventura, A. (1999). Glucose tolerance during pregnancy and birth weight in a Hispanic population. *Obstetrics and Gynecology, 94*, 741–746.

Langer, O., Brustman, L., Anyaegbunam, A., & Mazze, R. (1987). The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. *American Journal of Obstetrics and Gynecology, 157*, 758–763.

Langer, O., Rodriguez, D. A., Xenakis, E. M., McFarland, M. B., Berkus, M. D., & Arrendondo, F. (1994). Intensified versus conventional management of gestational diabetes. *American Journal of Obstetrics and Gynecology, 170*, 1036–1046 (discussion 1046–1047).

Lauszus, F. F., Paludan, J., & Klebe, J. G. (1999). Birthweight in women with potential gestational diabetes mellitus—an effect of obesity rather than glucose intolerance? *Acta Obstetricia et Gynecologia Scandinavica, 78*, 520–525.

Leikin, E. L., Jenkins, J. H., Pomerantz, G. A., & Klein, L. (1987). Abnormal glucose screening tests in pregnancy: a risk factor for fetal macrosomia. *Obstetrics and Gynecology, 69*, 570–573.

Lucas, M. J., Lowe, T. W., Bowe, L., & McIntire, D. D. (1993). Class A1 gestational diabetes: a meaningful diagnosis? *Obstetrics and Gynecology, 82*, 260–265.

Mello, G., Parretti, E., Mecacci, F., Lucchetti, R., Lagazio, C., Pratesi, M., & Scarselli, G. (1997). Risk factors for fetal macrosomia: the importance of a positive oral glucose challenge test. *European Journal of Endocrinology, 137*, 27–33.

Moses, R. G., & Griffiths, R. D. (1995). Can a diagnosis of gestational diabetes be an advantage to the outcome of pregnancy? *Journal of the Society for Gynecologic Investigation, 2*, 523–525.

Nasrat, H., Fageeh, W., Abalkhail, B., Yamani, T., & Ardawi, M. S. (1996). Determinants of pregnancy outcome in patients with gestational diabetes. *International Journal of Gynaecology and Obstettrics, 53*, 117–123.

SAS Institute Inc. (1999). *The SAS system for Windows release 8.0.* Carry, NC, USA.

Sermer, M., Naylor, C. D., Farine, D., Kenshole, A. B., Ritchie, J. W., Gare, D. J., Cohen, H. R., McArthur, K., Holzapfel, S., & Biringer, A. (1998). The Toronto Tri-Hospital Gestational Diabetes Project. A preliminary review. *Diabetes Care, 21*, B33–B42.

Snyder, J., Gray-Donald, K., & Koski, K. G. (1994). Predictors of infant birth weight in gestational diabetes. *American Journal of Clinical Nutrition, 59*, 1409–1414.

Verma, A., Mitchell, B. F., Demianczuk, N., Flowerdew, G., & Okun, N. B. (1997). Relationship between plasma glucose levels in glucose-intolerant women and newborn macrosomia. *Journal of Maternal–Fetal Medicine, 6*, 187–193.

Yang, X., Hsu-Hage, B., Dong, L., Shao, P., Wang, H., Tian, H., Chen, Y., & Zhang, H. (2003). Intensive diabetes management may improve pregnancy outcomes in Chinese gravidas with impaired glucose tolerance (letter). *Diabetes Care, 26*, 254–255.

Yang, X., Hsu-Hage, B., Dong, L., Zhang, C., & Zhang, Y. (2003). Postpartum glucose intolerance in Chinese women with gestational diabetes (letter). *Diabetic Medicine*, (in press).

Yang, X., Hsu-Hage, B., Yu, L., & Simmons, D. (2002). Selective screening for gestational diabetes in Chinese women (letter). *Diabetes Care, 25*, 796.

Yang, X., Hsu-Hage, B., Zhang, H., Yu, L., Dong, L., Li, J., Shao, P., & Zhang, C. (2002). Gestational diabetes mellitus in women of single gravidity in Tianjin city, China. *Diabetes Care, 25*, 847–851.

Yang, X., Hsu-Hage, B., Zhang, H., Zhang, C., Zhang, Y., & Zhang, C. (2002). Women with impaired glucose tolerance during pregnancy have significantly poor pregnancy outcomes. *Diabetes Care, 25*, 1619–1624.

et al., 1993). To maintain glycemic control, a combination of several kinds of treatments—including diet regulation, oral medication, and/or insulin treatment—is needed for DM patients. Large prospective studies have shown that persons with DM are at an increased risk of developing dementia, including Alzheimer's disease, particularly when treated with insulin (Ott et al., 1996, 1999). However, the effects of various treatments on cognitive function in DM patients have not been well investigated. For example, there has been only one study—that of Jagusch, Cramon, Renner, & Hepp, 1992—on the effect of treatment in nondemented DM patients; the results showed that insulin-treated subjects had slower simple reaction times. Recently we investigated the effect of treatment on the brain atrophy in elderly DM subjects, and found that the insulin-treated group had the most severe atrophy (Ushida et al., 2001).

Given this situation, the present study was initiated with the following three goals. First, we compared the domains of cognitive functional tests in elderly Japanese subjects (age >60 years) with type 2 DM with a group of elderly non-DM subjects (age >60 years). Second, we wanted to determine whether there was any correlation between the measures of cognitive function and the degree of glycemic control in patients with type 2 DM. Third, we investigated the effect of DM treatment on the performance of cognitive function tests.

2. Subjects and methods

2.1. Subjects

There were 69 subjects with type 2 DM and 27 non-DM subjects. All subjects were outpatients at Nagoya University Hospital in Aichi, Japan, at Gifu Prefectural Tajimi Hospital in Gifu, Japan, at Chiaki Hospital in Aichi, Japan, or at Aoki Kinen Hospital in Mie, Japan. They ranged in age from 60 to 85 years old. All subjects with diagnosis of dementia, depressive disorders by the clinical criteria defined by DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994), respectively, or any other diseases known to affect cognitive function, or subjects who had cerebral infarctions of more than 1 cm in diameter as visualized by brain CT or MRI, and/or had neurological sings or symptoms, and/or clinical histories of stroke including transient ischemic attacks were excluded. No subjects had audio–visual deficiencies sufficient to impair their performance in the cognitive functional assessments. All participants were independent in terms of performing their daily activities.

An ethical committee approved the study protocol and all patients gave their written informed consent prior to the investigation. After the provision of informed consent, the cognitive functional tests were administered individually to each subject. HbA1c was measured as a marker of glycemic control. DM patients were asked if they had had any hypoglycemic episodes during the recent month over the last month by questionnaire. At the day of the assessment subjects had breakfast as usual and the assessment was performed before noon. The doctors checked the physical conditions of the subjects before the assessment and confirmed that they were not hypoglycemic. Hypertension was diagnosed as follows: prescription of antihypertensive medicine, systolic blood pressure (SBP) of 160 mm Hg or higher, and/or diastolic blood pressure (DBP) of 95 mm Hg or higher. The diagnosis of hyperlipidemia was based on the *Japan atherosclerosis society guidelines for diagnosis and treatment of atherosclerotic cardiovascular disease* (Japan Atherosclerosis Society, 2002). Regarding complications of

Table 1
Characteristics of participants by diabetes status

Variable	DM subjects	Non-DM subjects	*P* value
N	69	27	–
Age	71.6 ± 5.6	73.4 ± 6.6	0.164
Gender (% female)	70.4	52.2	0.107
Education (years)	10.4 ± 2.7	11.4 ± 3.0	0.167
Hypertension (%)	52.5	50.0	0.845
Hyperlipidemia (%)	36.5	60.0	0.074
HbA1c (%)	8.0 ± 1.0	5.7 ± 0.4	$P<.01$

Data are the mean ± S.D. unless otherwise indicated.
Student's unpaired *t*-test (age, education, HbA1c) and Kruskal–Wallis analysis (other variables).

Table 2
Performance on measures of cognitive function by diabetes status

Measure	DM subjects	Non-DM subjects	*P* value
MMSE	27.1 ± 2.2	28.3 ± 1.7	$P<.05$
Word List (immediate)	5.7 ± 1.7	6.2 ± 1.7	0.254
(delayed)	7.1 ± 2.2	6.7 ± 2.0	0.364
WAIS-R Digit Symbol	36.3 ± 10.9	43.0 ± 12.1	$P<.05$
Stroop Color Word Test	19.2 ± 12.8	15.0 ± 6.7	0.113

Data are the means ± S.D., unless otherwise indicated.
A higher score indicates better performance, except in the case of the Stroop Color Word Test.
Student's unpaired *t*-test.
WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 3
Correlation coefficients between scores of cognitive tests and diabetic characteristics

Variables	MMSE	WAIS-R
WAIS-R Digit Symbol	0.456**	–
Diabetes duration	0.078	−0.155
HbA1c	−0.205	−0.433**
Neuropathy	−0.075	0.005
Nephropathy	−0.008	−0.021
Retinopathy	−0.095	0.015
Hypoglycemia	−0.265	−0.229
Insulin-treatment	−0.379**	−0.304*

Pearson's correlation coefficients analysis (MMSE, WAIS-R digit symbol, Diabetes duration HbA1c) and Spearman's correlation coefficients analysis (other variables).
* $P<.05$.
** $P<.01$.