nih.gov/SNP/snp_ref.cgi?locusId = 5663 and the PS-2 gene; http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId = 5664). We identified an entirely novel APP gene mutation (2032 G/A D678N [APP770 numbering]) in an early-onset FAD pedigree containing 3 affected members with a mean age of onset of 59.7 years and APOE genotype ε3/ε3.

Discussion

In the present study, we systematically conducted mutation screening of the PS-1, PS-2 and APP genes in samples from patients diagnosed with varied forms of AD. No pathogenic mutations of the PS-1 or PS-2 genes were identified. In the APP gene, we identified a novel mutation (D678N) in an early-onset FAD pedigree. This mutation is equivalent to an amino acid substitution of Asp at position 7 of amyloid-β (Aβ) (Asp7-Aβ) with Asn (Asn7-Aβ). We hypothesize that Asn7-Aβ derived from the D678N mutant APP has altered fibrillogenic and/or catabolic properties that increase accumulation of protein and/or the neurotoxic potential of Aβ, eventually leading to AD. In vitro studies will be necessary to characterize the pathogenic impact of the D678 mutation on fibrillogenesis and/or secretase activity.

We identified 2 novel SNPs in the APP gene and 9 SNPs (including 1 novel SNP) in the PS-2 gene. The IVS17-10 T/C polymorphism of the APP gene, identified from an EOSAD patient (age of onset: 59 years), is close to a splicing acceptor site and may raise a possibility to influence splicing efficiency. The genetic case-control study of this polymorphism is currently under way. While 861 C/T (P287P) polymorphism of the PS-2 gene was found in an FAD pedigree of variable age of onset (age 63–75), we have not obtained sufficient segregation data regarding this mutation. Furthermore, since 861 C/T (P287P) is a silent polymorphism, it is unclear whether this polymorphism (or a linked mutation) of the PS-2 gene contributes to the development of this FAD pedigree.

Genetic linkage studies have demonstrated multiple susceptible loci for FAD [22–26]. Additional studies are required to identify as many candidate genes as possible to elucidate the pathomechanisms of AD and improve our strategies for treatment and prevention of AD.

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Yosuke Wakutani
Department of Neurology, Institute of Neurological Sciences
Faculty of Medicine, Tottori University
Nishimachi 36–1, Yonago, Tottori 683–8504 (Japan)
Tel. +81 859 34 8034, Fax +81 859 34 8083, E-Mail ywaku@grape.med.tottori-u.ac.jp

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Oxidative Stress in Alzheimer Disease: The Earliest Cytological and Biochemical Feature

Akihiko Nunomura[a], *Shigeru Chiba*[a], *Atsushi Takeda*[b], *Mark A. Smith*[c], *George Perry*[c]

[a] Department of Psychiatry and Neurology, Asahikawa Medical College, Asahikawa,
[b] Department of Neurology, Tohoku University School of Medicine, Sendai, Japan,
[c] Institute of Pathology, Case Western Reserve University, Cleveland, Ohio, USA

Alzheimer Disease and Its Pathological Hallmarks

Alzheimer disease (AD) is defined pathologically by amyloid-β (Aβ) senile plaques and neurofibrillary tangles (NFTs) composed of tau. From the time of their original description, nearly a century ago, a major focus has been to understand the role that these lesions play in the pathogenesis of AD. Although senile plaques and NFTs are pathological hallmarks of AD, it is still questionable whether these pathological alterations cause associated neurodegeneration or behavioral and cognitive deficits that accompany the disease. Senile plaques and NFTs are present in a considerable percentage of brains of cognitively normal elderly subjects. Surprisingly, a study investigating autopsied subjects aged between 69 and 100 who were cognitively normal revealed that 49% of those normal subjects met the Khachaturian criteria for AD based on senile plaque density, 25% met the CERAD criteria based on senile plaque density, and 24% were in stages IV–VI of the Braak and Braak staging of AD based on NFT density [1]. Furthermore, it is well known that there is no correlation or a poor correlation between neuronal loss and senile plaque density as well as between disease severity and senile plaque density in AD [2]. By contrast, neuronal loss and clinical severity correlate with NFT density; however, the amount of neuronal loss largely exceeds the amount of

NFTs [3]. Indeed, neurons with NFTs are estimated to be able to survive for decades [4], which suggests that NFTs themselves are not obligatory for neuronal death in AD.

Therefore, senile plaques and NFTs may not be indispensable for death of vulnerable neurons in AD. We cannot exclude the possibility that the processes of senile plaques and NFTs formation are involved in compensatory changes of the aging brain against the pathogenesis of AD [5].

Aging, Oxidative Stress, and Alzheimer Disease

AD is a disease with a prevalence that increases exponentially throughout aging, with about half of the population afflicted by the age of 95 [6], which strongly supports an association between advancing age and AD. As in other organ systems, cells in the brain encounter a cumulative burden of oxidative and metabolic stress that may be a universal feature of the aging process as well as a major causal factor of senescence. Each of the macromolecules including nucleic acids, proteins, and lipids, is oxidatively modified during aging. Indeed, the brain is especially vulnerable to free radical damage because of its high oxygen consumption rate, abundant lipid content, and relative paucity of antioxidant enzymes compared with other organs [7, 8].

One gene that appears to have an influence on aging in general as well as on the risk of AD is apolipoprotein E (APOE). Individuals with an APOE4 allele have a reduced life span [9] and are at risk of AD [10]. Interestingly, APOE shows allele-specific antioxidant activity, with APOE2 being the most effective and APOE4 being the least effective, which suggests a link between oxidative stress and AD [11]. Actually, in autopsied brains with AD, there are increases in lipid peroxidation, protein oxidation, and DNA oxidation. The representatives of these oxidized products demonstrated in AD are 4-hydroxynonenal, protein carbonyls, and 8-hydroxydeoxyguanosine, respectively [12]. In 1999, we reported increased RNA oxidation in AD by in situ demonstration of an oxidized nucleoside derived from RNA, 8-hydroxyguanosine (8OHG) in vulnerable neurons of AD [13]. A significant increase in 8OHG in vulnerable neurons has also been demonstrated in Parkinson disease and Lewy body dementia, where increases in oxidized products of lipid, protein, and DNA have been shown as well [14, 15]. Certainly, oxidative stress is not a specific feature of AD but a common feature of age-associated neurodegeneration. One would expect that this oxidative damage is a common final product resulting from various pathways of neurodegeneration, but this is not the case, at least in AD.

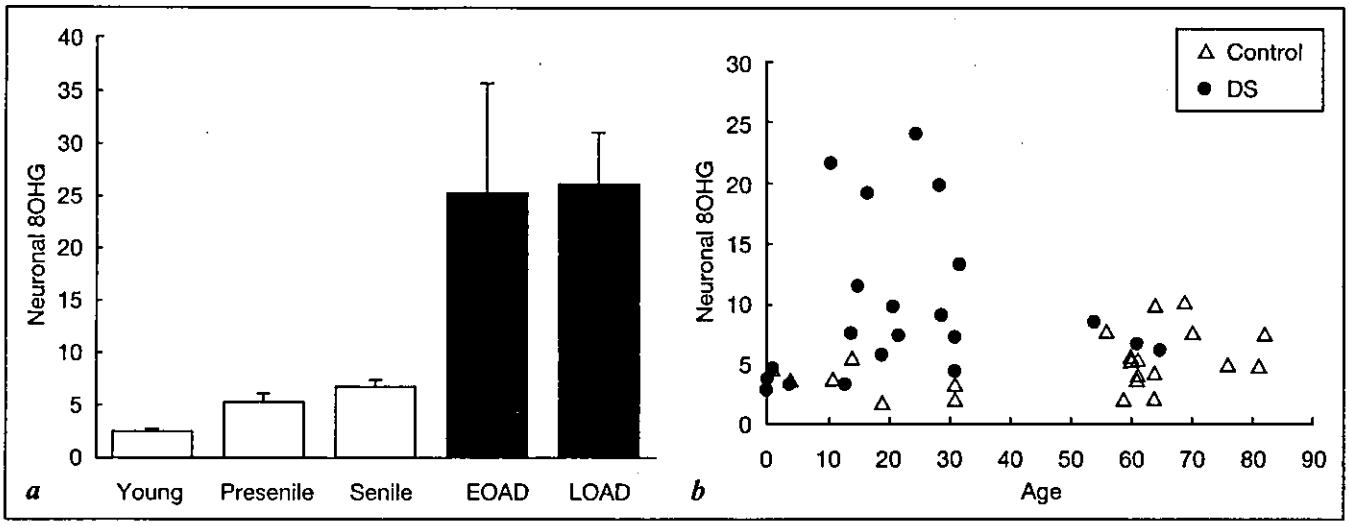

Fig. 1. Relative scale of 8OHG immunoreactivity with 1F7 antibody in AD and DS. Details of the methods for semiquantitative image analysis were described previously [13]. ***a*** The hippocampal subiculum neurons of 27 controls (4 young controls, 10 presenile controls, and 13 senile controls) and 16 cases with AD, i.e. 4 cases of early-onset AD (EOAD) and 12 cases of late-onset AD (LOAD), were examined. Values shown are the means with SE. The difference among all groups is significant by ANOVA ($p < 0.0001$) with post hoc analysis showing significant differences between each control group and EOAD as well as between each control group and LOAD. ***b*** Neurons in layer III of the occipitotemporal gyrus of 23 controls and 22 cases with DS were examined. Individuals with DS show elevation in neuronal 8OHG in their teens and twenties, while controls maintain low levels of neuronal 8OHG between the ages of 4 months and 82 years. In cases with DS, ANOVA followed by post hoc analysis reveals significantly higher 8OHG levels in age groups of the second and third decades compared with the first decade ($p < 0.01$).

Oxidized RNA Nucleoside: A Marker for Steady-State Levels of Oxidative Stress

We selected an in situ approach to identify the oxidized nucleoside 8OHG in AD brains. Immunocytochemically, neurons exhibiting marked immunoreactivity with 8OHG in the cytoplasm were widely distributed in the hippocampal region and cerebral neocortex, whereas neuronal cytoplasm was immunolabeled only faintly in controls. Relative intensity measurements of neuronal 8OHG immunoreactivity showed that there was a significant increase in nucleic acid oxidation in AD compared with controls (fig. 1a). Treatment with nuclease (DNase or RNase) before the immunostaining demonstrated that RNA was a major site of nucleic acid oxidation in AD [13], which was further supported by immunolabeling with ribosomal structures in immunoelectron microscopy for

8OHG [16]. Importantly, we found completely overlapping distributions of neurons showing increased 8OHG and other oxidative stress markers, such as mitochondrial DNA deletion detected with in situ hybridization as well as nitrotyrosine, a protein modification, detected with immunocytochemistry [16]. Because there is no evidence that 8OHG and nitrotyrosine, a non-crosslink protein adduct, are accumulated in cells, the levels of these oxidative markers are expected to reflect steady-state balance rather than a history of oxidative damage [17]. Therefore, an evaluation of the relative levels of these oxidative markers in vulnerable neurons in cases of AD with histopathological alterations of various severity enables us to investigate the relationship between oxidative stress and histological alterations.

Oxidative Stress: The Earliest Event in Alzheimer Disease

To determine whether oxidative stress is an early- or end-stage event in the process of neurodegeneration in AD, we investigated the relationship between the levels of oxidative damage and the extent of Aβ plaques and NFT formation, as well as the duration of dementia. Immunocytochemistry revealed that the levels of neuronal 8OHG and nitrotyrosine, markers of RNA and protein oxidation, were parallel in AD cases [16]. When we measured the area covered by Aβ deposition by image analysis, surprisingly, we found that increases in Aβ deposition were associated with decreased oxidative damage in neurons. Furthermore, a similar pattern of decrease in neuronal 8OHG was noted with increasing disease duration [16]. Moreover, when we investigated the effect of NFTs on the relative amount of 8OHG in neurons, we found that neurons with NFTs showed a 40–60% decrease in relative 8OHG levels compared with neurons free of NFTs [16]. These observations indicate that increased RNA oxidation and protein oxidation are early events in AD.

The early involvement of oxidative stress in the pathological cascade of AD is further supported by an investigation of a series of Down syndrome (DS) brains, in which an AD-like neuropathology is observed as an invariable feature starting in early adulthood. Double immunostaining with 8OHG and Aβ in cases of DS of various ages revealed that strong immunoreaction with 8OHG in neurons was observed in their teens and twenties, whereas the 8OHG immunoreactivity actually decreases with increasing Aβ deposition [18]. Semiquantitative analysis of neuronal 8OHG immunoreactivity and extent of Aβ burden demonstrated that, as a function of age, individuals with DS showed significant elevations in 8OHG in their teens and twenties but showed decreased 8OHG after 30 (fig. 1b), coincident with the accumulation of Aβ. These findings suggest that increased RNA oxidation occurs prior to the onset of Aβ deposition.

In concordance with our data from postmortem brain samples, cerebrospinal fluid from patients with AD showed not only significantly increased levels of 8OHG compared with controls but also greater elevation of 8OHG with shorter disease duration [19]. Furthermore, a recent study using a transgenic mouse model of AD supported the temporal primacy of oxidative stress versus Aβ deposition; in this model, increased lipid peroxidation preceded Aβ plaque formation in a transgenic mouse overexpressing a human AβPP transgene with a double Swedish mutation [20]. Biochemical analyses revealed that levels of urinary and plasma isoprostane, a product of lipid peroxidation were significantly higher in the transgenic than in the wild-type animals as early as 8 months of age. Increased levels of isoprastane were found as well from the age of 8 months in brain homogenates of the total brain cortex or hippocampus but not of the cerebellum. In contrast, pathologically, Aβ plaque formation occurred at 12 months of age in this animal model. The same research group investigated the levels of isoprostane in urine, plasma, and cerebrospinal fluid samples from subjects with AD and mild cognitive impairment (MCI) [21]. In all kinds of samples, levels of isoprostane were significantly higher in MCI than in controls, and significantly higher in AD than in MCI. The rate of progression from MCI to AD is estimated at approximately 12% per year, supporting the concept that MCI, at least in part, represents the prodromal stage of AD. Therefore, the oxidative stress is involved very early or in the preclinical stage of the pathological cascade of AD.

Oxidative Stress: An Attractive Therapeutic Target of Alzheimer Disease

With the notion that increased oxidative stress is one of the earliest changes in the pathogenesis of AD, it is not surprising that agents inhibiting free radical formation reduce both the incidence and the progression of AD. Agents such as vitamin E, selegiline, *Gingko biloba*, estrogen, and nonsteroidal anti-inflammatory drugs have been proven to have an antioxidant activity and to reduce the incidence and/or the rate of progression of AD [22]. According to two recent prospective epidemiological cohort studies [23, 24], higher dietary intake of antioxidants, especially vitamin E, was associated with a lower risk of AD. However, when we consider the complicated system of the fine regulation of cellular redox balance in human body, it is no wonder that extrinsic in vitro antioxidants may show only limited effects on the reduction of oxidative damage in biological systems. In fact, well-known dietary antioxidants such as carotenoids as well as flavonoids can act as prooxidants in certain experimental conditions [25, 26]. Therefore, we should find ways of activating

our intrinsic system in order to reduce oxidative damage, which might effectively slow down disease progression, at least in the subclinical and early stage of AD.

It is well known that experimental animals on dietary restriction that lowers steady-state levels of oxidative stress show various signs of retarded aging [27]. Recently, the association between caloric intake and the risk of AD was reported [28]. Compared with individuals in the lowest quartile of total calorie or fat intake, those in the highest quartile had an increased risk of AD. This increased risk was significant only among individuals carrying the APOE4 allele. The hazard ratios of AD for total calorie intake and fat intake are 2.27 and 2.31, respectively. A life-style-related factor other than diet, i.e. lack of exercise is considered to be a risk factor for AD. Friedland et al. [29] evaluated passive, intellectual, and physical activities by using a scale in terms of 'diversity', expressed in total number of activities, and in terms of 'intensity', expressed in hours per month. In patients with AD, the scores were significantly lower in passive diversity, intellectual diversity, and physical diversity as well as in intellectual intensity in early and middle adulthood. Mattson et al. [8] suggest that dietary restriction, intellectual activity, and exercise promote neuronal survival through decreased oxidative stress. They argue that each of them induces mild cellular stress responses, and consequently neurons respond to these stresses by activating on signaling pathways that produce growth factors and protein chaperones. These aspects may be important to prevent AD or at least delay its onset, especially in subjects at high risk of developing AD, such as APOE4 carriers.

Conclusion

The early involvement of oxidative stress in the pathogenesis of AD is supported by cytological and biochemical analyses of human brain samples of AD, DS and MCI as well as a transgenic animal model of AD. Therefore, reducing oxidative stress is an attractive therapeutic target, especially in subjects at high risk of developing AD, such as APOE4 carriers. Not only intake of antioxidants but also calorie restriction as well as maintaining intellectual and physical activities are possible strategies against oxidative stress.

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Akihiko Nunomura, MD, PhD
Department of Psychiatry and Neurology, Asahikawa Medical College
Higashi 2–1–1–1, Midorigaoka, Asahikawa 078–8510 (Japan)
Tel. +81 166 68 2473, Fax +81 166 68 2479, E-Mail nuno@asahikawa-med.ac.jp

最新医学・別冊　新しい診断と治療のABC 22　(別刷)

神経 3　アルツハイマー病

アルツハイマー病の診断

評価スケール

浦 上 克 哉　　谷 口 美也子

最 新 医 学 社

第3章　アルツハイマー病の診断

評価スケール

要旨

現在アルツハイマー病の診断の際，判断材料の一つとして汎用されている評価スケールを本稿では概説する．評価スケールを，スクリーニング検査，詳細な神経心理学的検査・高次機能検査のためのスケール，観察式認知機能評価スケール，その他のスケールに分けて特徴を解説する．さらに，新規スクリーニング法としてタッチパネル式コンピューターを用いたアルツハイマー病の簡易スクリーニング法を紹介する．アルツハイマー病の早期診断のための簡易スクリーニング法と確定診断に役立つ有用な評価スケールが望まれる．

● キーワード

痴呆
観察式
質問式
スクリーニング
タッチパネル式コンピューター

はじめに

現在アルツハイマー病の診断は，各種の診断基準に合致するか否かで行っている．その際の判断材料の一つとして汎用されているものに評価スケールが存在する．本稿では各種の評価スケールを紹介し，その利点，欠点，使い方のポイントについて概説する．

1．スクリーニング検査

スクリーニング検査として用いる評価スケールとして代表的なものに，長谷川式簡易知的機能検査—改訂版（HDS－R），ミニメンタルステート検査（MMSE）がある．共にスクリーニングを目的としたスケールで日常診療の中で汎用されている．HDS－R は本邦で作成されたものであり，MMSE は欧米で作成されたものである．HDS－R の特徴としては，最後の問題で言葉の流暢性を調べる検査があり，これは前頭葉の機能を反映する実行機能を見ており，これが MMSE にはない．一方 MMSE は，図形の模写や文章作成などの動作性検査が含まれている点が特徴である．ただ，図形の模写が，平面図形であるため平易であり，軽度の構成失行を検出できない．

表1　アルツハイマー病評価スケール（ADAS）

ADAS-Jcog 採点表

検査日：　　年　　月　　日　　患者名：　　男・女　　歳
検査者：　　所要時間：　　分
その他観察：

項目	評価基準	得点
1．単語再生*	正解数［①＿＿＿②＿＿＿③＿＿＿平均　　］10－　（平均正解数）	
2．口頭言語能力	0：全く支障なし　1：ごく軽度　2：軽度　3：中程度　4：やや重度　5：重度	
3．言語の聴覚的理解	0：全く支障なし　1：ごく軽度　2：軽度　3：中程度　4：やや重度　5：重度	
4．自発語における喚語困難	0：全く支障なし　1：ごく軽度　2：軽度　3：中程度　4：やや重度　5：重度	
5．口頭命令に従う	各段階の正確数：□1段階　□2段階　□3段階　□4段階　□5段階 従えた命令の数［　　］5－　（平均正解数）	
6．手指および物品呼称	（不正解の数） 0：0～2　1：3～5　2：6～8　3：9～11　4：12～14　5：15～17	
7．構成行為（描画） （不正解な図形の数）	図形の正確性：□円　□2つの長方形　□ひし形　□立方体 なぞり書き　：□なし　□あり	
	0：0（すべて正解）1：1　図形のみ　2：2　図形 3：3図形　4：4図形またはなぞり書き，囲い込み　5：書かれていない	
8．観念運動	（一括教示時に達成できた動作） □1段階　□2段階　□3段階　□4段階　□5段階 一括教示でできた動作の数［　　］5－　（平均正解数）	
	（部分教示の有無）□なし　□あり □1段階　□2段階　□3段階　□4段階　□5段階	
	（部分教示時に達成できた動作） □1段階　□2段階　□3段階　□4段階　□5段階	
9．見当識	正解数［　　］8－　（平均正解数）	
10．単語再認*	正解数［①＿＿＿②＿＿＿③＿＿＿平均　　］12－　（平均正解数）	
11．テスト教示の再生能力	0：全く支障なし　1：ごく軽度　2：軽度　3：中程度　4：やや高度　5：高度	
合計得点	（得点範囲：0～70）	/70

*単語再生と単語再認は小数点以下第2位を四捨五入して第1位までを記入する．

表2 ウェクスラー成人知能評価スケール改訂版（WAIS-R）

Wechsler Adult Intelligence Scale Revised（WAIS-R）

検査日：　年　月　日　患者名：　男・女　歳
職業：　最終学歴：　所要時間：　時間　分
検査者：
その他観察：

言語性検査		動作性検査	
	粗点　評価点（SS）		粗点　評価点（SS）
1	知識	2	絵画完成
3	数唱	4	絵画配列
5	単語	6	積木模様
7	算数	8	組合せ
9	理解	10	符号
11	類似		
言語性評価点合計（VSS）		動作性評価点合計（PSS）	

VIQ	PIQ	IQ

略語：巻末の略語集参照

2．詳細な神経心理学的検査・高次機能検査のためのスケール

1）アルツハイマー病評価スケール（ADAS）

新薬の治験や薬物療法の効果判定に国際的に用いられている検査である（表1）[1]．認知機能検査（ADAS cog）と非認知機能検査（ADAS non cog）から成り，認知機能検査には，① 単語再生，② 口頭言語能力，③ 言語の聴覚的理解，④ 自発語における換語困難，⑤ 口頭命令に従う，⑥ 手指および物品呼称，⑦ 構成行為，⑧ 観念運動，⑨ 見当識，⑩ 単語再認，⑪ テスト教示の再生能力，の 11 の尺度から評価項目がある．非認知機能検査には，① 涙もろさ，② 抑うつ気分，③ 集中力の欠如，④ 検査に対する協力度，⑤ 妄想，⑥ 幻覚，⑦ 徘徊，⑧ 多動，⑨ 振戦，⑩ 食欲の亢進・減少，の 10 の尺度から成っている．アルツハイマー型痴呆の治療の治験には ADAS cog のみが独立して使用されることが多い．満点は 70 点（全く答えられない場合）で，15 点は MMSE 26 点相当と考えられる．施行は約 30

表3 機能評価ステージ（FAST）

Functional Assessment Staging（FAST）

検査日：　　年　　月　　日　　患者名：　　男・女　　歳

FAST stage	臨床診断	FAST の特徴	臨床的特徴
1．認知機能障害なし	正常	主観的および客観的機能低下は認められない．	5～10 年前と比較して職業あるいは社会生活上，主観的および客観的にも変化は全く認められず支障を来すこともない．
2．非常に軽度の認知機能低下	年齢相応	物の置き忘れを訴える．喚語困難．	名前や物の場所，約束を忘れたりすることがあるが年齢相応の変化であり，親しい友人や同僚にも通常は気がつかれない．複雑な仕事を遂行したり，込み入った社会生活に適応していくうえで支障はない．多くの場合，正常な老化以外の状態は認められない．
3．軽度の認知機能低下	境界領域	熟練を要する仕事の場面では機能低下が同僚によって認められる．新しい場所に旅行することは困難．	重要な約束を忘れてしまうことがある．初めての土地への旅行のような複雑な作業を遂行する場合には，機能低下が明らかになる．買い物や家計の管理あるいはよく知っている場所への旅行など日常行っている作業をするうえで支障はない．熟練を要する職業や社会的活動から退職してしまうこともあるが，その後の日常生活の中では障害は明らかとはならず，臨床的には軽微である．
4．中等度の認知機能低下	軽度のアルツハイマー病	夕食に客を招く段取りを付けたり，買い物をしたりする程度の仕事でも支障を来たす．	買い物で必要な物を必要な量だけ買うことができない．誰かがついて行かないと買い物の勘定を正しく払うことができない．自分で洋服を選んで着たり，入浴したり，行き慣れている所へ行ったりすることには支障はないために日常生活では介助を要しないが，社会生活では支障を来たすことがある．単身でアパート生活している老人の場合，家賃の額で大家とトラブルを起すようなことがある．
5．やや重度の認知機能低下	中等度のアルツハイマー病	介助なしでは適切な洋服を選んで着ることができない．入浴させるときにも何とかなだめすかして説得することが必要なこともある．	家庭での日常生活でも自立できない．買い物を1人ですることはできない．季節に合った洋服が選べず，明らかに釣り合いがとれていない組み合わせで服を着たりするために，きちんと服をそろえるなどの介助が必要となる．毎日の入浴を忘れることもある．なだめすかして入浴させなければならない．自分で体をきちんと洗うことができるし，お湯の調節もできる．自動車を適切かつ安全に運転できなくなり，不適切にスピードを上げたり下げたり，また，信号を無視したりする．無事故だった人が初めて事故を起すこともある．大声をあげたりするような感情障害や多動，睡眠障害によって家庭で不適応を起し医師による治療的かかわりがしばしば必要になる．

6．重度の認知機能低下	やや重度のアルツハイマー病	(a) 不適切な着衣	寝間着の上に普段着を重ねて着てしまう．靴紐が結べなかったり，ボタンを掛けられなかったり，ネクタイをきちんと結べなかったり，左右間違えずに靴を履けなかったりする．着衣も介助が必要になる．
		(b) 入浴に介助を要する．入浴を嫌がる．	お湯の温度や量の調節ができなくなり，体もうまく洗えなくなる．浴槽への出入りもできにくくなり，風呂から出た後もきちんと体を拭くことができない．このような障害に先行して風呂に入りたがらない，嫌がるという行動が見られることもある．
		(c) トイレの水を流せなくなる．	用を済ませた後，水を流すのを忘れたり，きちんと拭くのを忘れる．あるいは済ませたあと服をきちんと直せなかったりする．
		(d) 尿失禁	時に（C）の段階と同時に起るが，これらの段階の間には数ヵ月の間隔があることが多い．この時期に起る尿失禁は，尿路感染や他の生殖器泌尿器系の障害がなく起る．この時期の尿失禁は，適切な排尿行動を行ううえでの認知機能の低下によって起る．
		(e) 便失禁	この時期の障害は，(c) や (d) の段階で見られることもあるが，通常は，一時的にしろ別々に見られることが多い．焦燥や明らかな精神病様症状のために医療施設を受信することも多い．攻撃的行為や失禁のために施設入所が考慮されることが多い．
7．非常に重度の認知機能低下	重度のアルツハイマー病	(a) 最大限約6個に限定された言語機能の低下	語彙と言語能力の貧困はアルツハイマー病の特徴であるが，発語量の減少と話し言葉のとぎれがしばしば認められる．さらに進行すると完全な文章を話す能力が次第に失われる．失禁が見られるようになると，話し言葉は幾つかの単語あるいは短い文節に限られ，語彙は2，3単語にのみ限られてしまう．
		(b) 理解しうる語彙はただ1つの単語となる	最後に残される単語には個人差があり，ある患者では“はい”という言葉が肯定と否定の両方の意志を示すときもあり，逆に“いいえ”という返事が両方の意味を持つこともある．病気が進行するに従って，このようなただ一つの言葉も失われてしまう．一見，言葉が完全に失われてしまったと思われてから数ヵ月後に突然最後に残されていた単語を一時的に発語することがあるが，理解しうる話し言葉が失われた後は叫び声や意味不明のぶつぶつ言う声のみとなる．
		(c) 歩行能力の喪失	歩行障害が出現する．ゆっくりとした小刻みの歩行となり階段の上り下がりに介助を要するようになる．歩行ができなくなる時期に個人差はあるが，次第に歩行がゆっくりとなり，歩幅が小さくなっていく場合もあり，歩くときに前方あるいは後方や側方に傾いたりする．寝たきりとなって数ヵ月すると拘縮が出現する．

（次頁へつづく）

		(d) 着座能力の喪失	寝たきりの状態であっても初めのうち介助なしで椅子に座っていることは可能である．しかし，次第に介助なしで椅子に座っていることもできなくなる．この時期ではまだ笑ったり，掴んだり，握ることはできる．
		(e) 笑う能力の喪失	この時期では刺激に対して眼球をゆっくり動かすことは可能である．多くの患者では把握反射は嚥下運動とともに保たれる．
		(f) 昏迷および昏睡	アルツハイマー病の末期とも言えるこの時期は，本疾患に付随する代謝機能の低下と関連する．

～60分かかり，多忙な日常診療の中で用いることはかなり難しい．

2）ウェクスラー成人知能評価スケール改訂版（WAIS－R）

IQが算出でき，言語性IQと動作性IQに分けて評価できる（表2）．高次機能評価のスケールとして信頼性が高いが，適用年齢が74歳までとなっており，痴呆性高齢者は75歳以上に多く見られ施行が限定される．また，施行に1～2時間要し，患者の負担が大きい欠点がある．

3．観察式認知機能評価スケール

前述の詳細な神経心理学的検査・高次機能検査は，高齢者には精神的にも肉体的にも負担が大きい．観察式検査はこのような欠点がなく有用である．ただ観察者に観察力が要求される．

1）精神機能障害スケール（MENFIS）

認知機能障害（場所の見当識，時間の見当識，最近の記憶，昔の記憶，会話理解の障害，意思表示の障害，判断の障害），動機付けの機能障害（自発性の障害，興味･感心の障害，気力の障害），感情機能障害（感情表現の多様性の障害，感情表現の安定性の障害，感情表現の適切性の障害）合計13項目について，0（全く障害なし）から6（完全な障害）までの7段階で評価する．

2）機能評価ステージ（FAST）

日常の行動の観察から重症度を評価するスケールであり，痴呆の病期を7段階に分類している（表3）[2]．重症度の指標となる症状が記載されており，比較的判断しやすく有用なスケールである．正常とは

表 4　臨床的痴呆評価（CDR）

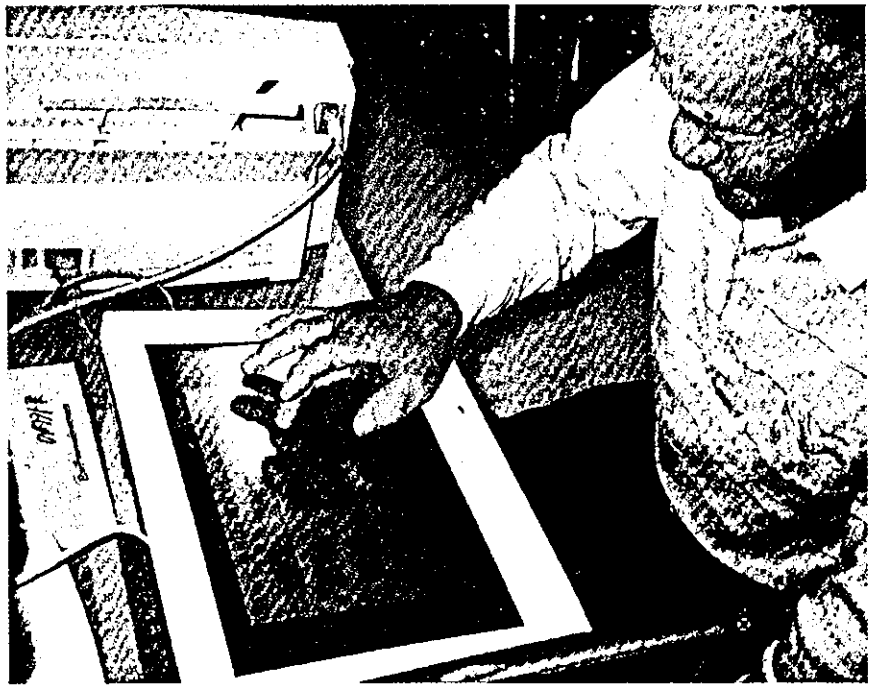
Clinical Dementia Rating（CDR）

検査日：　年　月　日　患者名：　男・女　歳

	健康 (CDR 0)	痴呆の疑い (CDR 0.5)	軽度痴呆 (CDR1)	中等度痴呆 (CDR2)	重症痴呆 (CDR3)
記憶	記憶障害なし 時に若干のもの忘れ	一貫した軽いもの忘れ 出来事を部分的に思い出す 良性健忘	中等度記憶障害，特に最近の出来事に対するもの 日常生活に支障	重度記憶障害 高度に学習した記憶障害は保持，新しいものはすぐに忘れる	重度記憶障害 断片的記憶のみ残存
見当識	見当識障害なし	同左	時間に対しての障害あり，検査では場所，人物の失見当なし，しかし時に地誌的失見当あり	常時，時間の失見当，時に場所の失見当あり	人物への見当識のみ
判断力と問題解決	適切な判断力，問題解決	問題解決能力の障害が疑われる	複雑な問題解決に関する中等度の障害 社会的判断力は保持	重度の問題解決能力の障害 社会的判断力の障害	判断不能 問題解決不能
社会適応	仕事，買い物，ビジネス，金銭の取り扱い，ボランティアや社会的グループで，普通の自立した生活	左記の活動の軽度障害もしくはその疑い	左記の活動の幾つかにかかわっていても，自立した機能が果せない	家庭内（一般社会）では独立した機能は果たせない	同左
家庭状況および趣味・関心	家での生活趣味，知的関心が保持されている	同左，もしくは若干の障害	軽度の家庭生活の障害 複雑な家事は障害 高度の趣味・関心の喪失	単純な家事のみに限定された関心	家庭内不適応
介護状況	セルフケア完全	同左	ときどき激励が必要	着衣，衛生管理などの身の回りのことに介助が必要	日常生活に十分な介護を要する しばしば失禁

総合 CDR ：＿＿＿＿＿＿

図1　痴呆簡易スクリーニングのためのタッチパネル式コンピューター



言えないが痴呆とも言えないという“境界状態”が分類されており，現在注目されている軽度認知障害（MCI）に相当するものと思われる．また，“重度”と“極めて重度”などを詳細に分類しているところも特徴である．

3）臨床的痴呆評価（CDR）

痴呆の重症度評価法の一つで，近年汎用されている（表4）[3]．評価項目は ① 記憶，② 見当識，③ 判断力と問題解決，④ 社会適応，⑤ 家庭状況および趣味・関心，⑥ 介護状況の6項目から成る．この6項目について5段階の評価を行った後，総合的な重症度を判定する．従来の判定方法が複雑であるため，近年簡易な判定方法が示されている．ちなみに，MCI は CDR 0.5 程度として評価されていることが多い．

4．その他のスケール

1）高齢者うつ病評価スケール（GDS）

高齢者うつ病のスクリーニングテストとして汎用されているスケールである[4]．痴呆症の診断に際し，うつ病との鑑別は重要であり，鑑別診断の一つの指標として用いられる．