Clinical Practice Guideline for Dementia
Part I: Diagnosis & Evaluation

Clinical Research Center for Dementia of South Korea
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Introduction

The developmental objectives of the Clinical Practice Guideline for Dementia

The prevalence of dementia in the elderly aged \( \geq 65 \) is 5-10\%, almost doubling with every 5-years in aging (John et al., 1987). Its prevalence in Korea was shown in a series of local epidemiological studies to range between 8.2-10.8\% (Park et al., 1994; Cho et al., 1998; Woo et al., 1998; Seo et al., 2000; Kim et al., 2000; Lee et al., 2002; Kim et al., 2003; The Korean Ministry of Health & Welfare, 2009). From the size of the Korean elderly population of 5.19 millions in 2009, the number of patients with dementia was inferred to be about 400,000 (The Korean Ministry of Health & Welfare, 2009), of whom approximately 30\% were receiving aggressive treatment (Kang et al., 2005).

Korea is one of the fastest aging countries across the globe. The elderly population aged \( \geq 65 \) is predicted to reach about 13.2\% of the total population by 2020, with the number of dementia patients soaring to 700,000 and thus causing a serious social problem (The National Statistics Office, 2003). In 2007, a total of 135,219 patients came to see a physician for symptoms of dementia, almost a 3-fold increase from 47,747 in 2002. The medical expenditure for dementia also increased from 56 billion KRW in 2002 to 326.8 billion KRW in 2007, a 5.8 fold rise over the 5 year period (The Korean National Health Insurance Corporation, 2007). The government responded by working out the Comprehensive Measures for Dementia Management, essentially focused on expanding the dementia screening program and providing financial support for treatment in low-income dementia patients (The Korean Ministry of Health & Welfare, 2008). Despite these efforts, early detection and treatment of dementia is still elusive partially due to the lack of systematic standard clinical practice guidelines for diagnosis and treatment of dementia. The Clinical Research Center for Dementia of South Korea (CREDOS) aims to achieve the following goals by developing a CPG for dementia that best addresses the local needs.

1. To establish evidence-based, objective and clear clinical standards for dementia.
2. To improve the clinical decision-making process for clinicians dealing with dementia patients.
3. To provide scientific and systematic scales to aid in the work of dementia specialists.
4. To suggest comprehensive and systematic healthcare service tailored to each dementia subtype.

Development of Clinical Practice Guideline for Dementia through adaptation

The CREDOS formed a development group (Fervers B et al., 2006) that worked from May 2007 to August 2009 to devise a locally customized CPG for dementia. The group agreed to accept adaptation as the core developmental method. Because Korea has no previously available domestic guideline for dementia, adaptation that modifies previously published acknowledged foreign guidelines can be an efficient alternative to de novo development of a new guideline. The ADAPTE Collaboration-suggested methodology for adaptation was used (Fervers B et al., 2006). In accordance with the Manual for Guideline Adaptation (Kim SY et al., 2009) development of a CPG for dementia followed a step-wise approach; Set-up, Adaptation, and Finalization phase (Table 1).
## Table 1. Development of CPG for dementia

<table>
<thead>
<tr>
<th>Phase</th>
<th>Module</th>
<th>Step</th>
<th>Tasks</th>
<th>Outputs</th>
<th>Developmental details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setup</td>
<td>Preparation</td>
<td>1</td>
<td>Formation of the steering committee</td>
<td>The CPG for dementia steering committee was formed with multi-disciplinary inputs from clinicians (neurologists and psychiatrists), search experts, methodology experts, and other stakeholders</td>
<td>Alzheimer disease (AD), vascular dementia (VaD), mild cognitive impairment (MCI), and vascular cognitive impairment (VCI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Subject determination</td>
<td>The subjects of CPG for dementia</td>
<td>The list was finalized.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Adaptation feasibility review</td>
<td>A list of the dementia related guidelines</td>
<td>The CPG for dementia development group was divided into the operating committee and the working committee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Formation of the working committee</td>
<td>The working committee CPG for dementia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>Planning task execution</td>
<td>Determination of authors for each chapter</td>
<td>Authors were chosen from the working committee.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>Dissemination and implementation strategies</td>
<td>The implementation strategies</td>
<td>Published as a review article in the Journal of the Korean Medical Association (KMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Documentation of adaptation plans</td>
<td>The CPG for dementia adaptation plan and the execution time table</td>
<td>Linked to the CREDOS, Korean Clinical Research Coordination Center and KMA websites</td>
</tr>
</tbody>
</table>

### Scope and goals

<table>
<thead>
<tr>
<th>Key questions</th>
<th>A list of the key questions</th>
<th>The scope and goals of the CPG for dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Scope and goals</td>
<td>Scope and key questions</td>
</tr>
<tr>
<td>3</td>
<td>Search and screening of source guidelines</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Source guideline assessment</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Guideline quality assessment</td>
<td>10</td>
</tr>
</tbody>
</table>
11 Guideline currency assessment
   A summary table for the currency of the selected guidelines
   Evaluation of the key guidelines based on the currency summary table

12 Guideline evidence assessment
   A summary table for the recommendations of the key guidelines
   Evaluation of validity of evidence, consistency of evidence and recommendations, and risk of bias

13 Assessment of acceptability and applicability of recommendations
   A summary table for consistency through the evidence, interpretations, and recommendations
   Evaluation of the acceptability and applicability of the recommendations

14 Review of assessment

15 Selection and modification of recommendations
   The draft of CPG for dementia recommendations
   Certain recommendations from the selected guidelines were modified.

16 Draft preparation
   The draft of CPG for dementia
   Preparation was based on the guideline writing principles and the recommendation modification report form

17 External review, stakeholder opinion gathering, and target user research
   Feedbacks and future measures
   Each subject of the draft CPG for dementia went through the process.

18 Request of the official endorsement
   A public hearing on the CPG for dementia
   Accreditation was made by dementia-related academic entities (the Korean Neuropsychiatric Association, the Korean Neurological Association, the Korean Dementia Association, and the Korean Association for Geriatric Psychiatry).

19 Sorting of the literature and references
   A follow-up meeting after the hearing
   Modification was made as pointed out at the hearing.

20 Plans for future review and update
   The CPG for dementia revision plan
   The revision plan was aimed at evaluation and supplementation of the developed CPG for dementia for additional guideline development and their evaluation and supplementation;

21 Writing of the final guideline
   The full text of the CPG for dementia
   Development of a CPG for treatment and management of AD, VaD, MCI, VCI

1. Set-up phase
   In the set-up phase, a guideline development group is formed and trained. An overall developmental strategy is also determined during this phase. The CPG for dementia development group consisted of psychiatric and neurological specialists as well as preventionists, search experts, and methodology experts.
For training, two workshops were held with guest speakers who had extensive experience in guideline development. They provided systematic insights into the strategies for guideline development, dissemination, and implementation. Participants also reviewed and discussed a number of different guideline developmental methodologies including de novo, translation and adaptation development. After a series of monthly meetings, the group decided to adopt an adaptation strategy (Table 2).

Table 2. Meetings of the CPG for dementia development group

<table>
<thead>
<tr>
<th>Date</th>
<th>Occasion</th>
<th>Venue</th>
<th>Discussed items</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2007</td>
<td>The 1st workshop</td>
<td>The meeting room at the Korean Neuropsychiatry Association, 8F, Samsung Medical Center, Training Center</td>
<td>Guidelines of brain imaging for dementia, Guideline writing tips</td>
</tr>
<tr>
<td>June 2007</td>
<td>The 1st CPG for dementia meeting</td>
<td>8F, Samsung Medical Center, Annex Building</td>
<td>Compilation of the CPG for dementia database booklets, Comparison of the existing guidelines for dementia</td>
</tr>
<tr>
<td>July 2007</td>
<td>The 2nd CPG for dementia meeting</td>
<td>8F, Samsung Medical Center, Annex Building</td>
<td>Distribution of the CPG for dementia database booklets, Task force team formation</td>
</tr>
<tr>
<td>August 2007</td>
<td>The 3rd CPG for dementia meeting</td>
<td>8F, Samsung Medical Center, Annex Building</td>
<td>Finalization of the scope and patient population, Adaptation methodology decided</td>
</tr>
<tr>
<td>September 2007</td>
<td>The 4th CPG for dementia meeting</td>
<td>8F, Samsung Medical Center, Annex Building</td>
<td>Presentation of literature search methodology, Determination of clinical questions for each item</td>
</tr>
<tr>
<td>October 2007</td>
<td>The 2nd workshop</td>
<td>Samsung Medical Center M2, Training Center</td>
<td>CPG for dementia development announced, Decision of adaptation for the CPG for dementia</td>
</tr>
<tr>
<td>November 2007</td>
<td>The 5th CPG for dementia meeting</td>
<td>8F, Samsung Medical Center, Annex Building</td>
<td>Presentation of the guideline development process for asthma in adults, Decision of the time lines for the CPG for dementia</td>
</tr>
<tr>
<td>January 2008</td>
<td>The 6th CPG for dementia meeting</td>
<td>1 BF, Samsung Medical Center, Cancer Center</td>
<td>Review of the diagnostic standards for VaD, Overall CPG for dementia outline determination, Publication method discussed</td>
</tr>
<tr>
<td>February 2008</td>
<td>The 7th CPG for dementia meeting</td>
<td>The Grand Intercontinental Hotel, Seoul</td>
<td>Overall review of CPG for dementia in the preparing</td>
</tr>
<tr>
<td>June 2008</td>
<td>The 8th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Overall review of CPG for dementia in the preparing, Decision to add more domestic data</td>
</tr>
<tr>
<td>July 2008</td>
<td>The 9th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Explanation of CPG for dementia to the The Korean Ministry of Health &amp; Welfare officers in charge of the elderly policy, Development of the ‘Recommendations for cognitive health in the Elderly’ announced</td>
</tr>
<tr>
<td>August 2008</td>
<td>The 10th CPG for dementia meeting</td>
<td>Samsung Medical Center M3, Training Center</td>
<td>Determination of the guideline format, Discussion of the need for CPG for dementia supplementation</td>
</tr>
<tr>
<td>September 2008</td>
<td>The 11th CPG for dementia meeting</td>
<td>Grand Hyatt Hotel, Seoul</td>
<td></td>
</tr>
<tr>
<td>October 2008</td>
<td>The 12th CPG for dementia meeting</td>
<td>1 BF, Samsung Medical Center, Cancer Center</td>
<td>Developers boarded together for completion and review of the preliminary CPG for dementia</td>
</tr>
<tr>
<td>November 2008</td>
<td>The 13th CPG for dementia meeting</td>
<td>Samsung Medical Center M3, Training Center</td>
<td>Review of the modified preliminary CPG for dementia, Revision and supplementation of the preliminary CPG for dementia</td>
</tr>
<tr>
<td>December 2008</td>
<td>The 14th CPG for dementia meeting</td>
<td>Samsung Medical Center M2, Training Center</td>
<td>Feedbacks on the preliminary CPG for dementia</td>
</tr>
<tr>
<td>February 2009</td>
<td>The 15th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Feedbacks on the preliminary CPG for dementia</td>
</tr>
<tr>
<td>March 2009</td>
<td>The 16th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Feedbacks on the preliminary CPG for dementia</td>
</tr>
<tr>
<td>April 2009</td>
<td>The 17th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Feedbacks on the preliminary CPG for dementia</td>
</tr>
<tr>
<td>May 2009</td>
<td>The 18th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Discussion of the methodology for the CPG for dementia hearing</td>
</tr>
<tr>
<td>June 2009</td>
<td>The 19th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Decision of the joint hearing organization with NCRC</td>
</tr>
<tr>
<td>August 2009</td>
<td>The 20th CPG for dementia meeting</td>
<td>2 BF, Samsung Medical Center, Cancer Center</td>
<td>Determination of the CPG for dementia accreditation societies</td>
</tr>
</tbody>
</table>
2. Adaptation Phase

The full adaptation process begins in earnest in this phase. We mainly used a methodology suggested by the ADAPTE Collaboration (Fervers B et al, 2006). First, the previously published appropriate source guidelines were examined. After searching the internet for published CPGs for dementias (primary database; Pubmed (Medline), Embase, and psycINFO, key words; clinical practice guideline and dementia) published during the period of 1997 and 2007, a total of 22 guidelines were retrieved. The data was compiled into a 1,399 page documentation presented in 3 separate booklets (Table 3); volume I: General guidelines for dementia (580 pages), volume II; Diagnosis guidelines for dementia (373 pages), and volume III; Treatment guidelines for dementia (446 pages). For data published after 2007, we first searched online using Pubmed (Medline), Embase, and psycINFO (key words; dementia or mild cognitive impairment) and came up with 251 systematic reviews, of which 152 review articles were preliminarily selected as additional literature. After review by the steering committee, 85 were finally included.

Table 3. The List of Source Guidelines of the CPG for dementia

<table>
<thead>
<tr>
<th>Publisher(Authors)</th>
<th>Title</th>
<th>Booklet(Article)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Royal Australian College of General Practitioners</td>
<td>Care of Patients with Dementia in General Practice Guidelines</td>
<td>North Sydney: NSW Department of Health, 2003</td>
</tr>
<tr>
<td>7 National Institute of Neurological Disorders and Stroke-Canadian Stroke Network</td>
<td>vascular cognitive impairment harmonization standards</td>
<td>Stroke. 2006;37:2220-2241</td>
</tr>
</tbody>
</table>
Overall review and comparison of the 22 guidelines presented in the booklets led to determination of the 4 selected guidelines for adaptation to the CPG for dementias. Selection was based on the Korean Guideline Instrument for Evaluation or K-GINE (Kim MS et al, NCRC, 2009). We adopted the AGREE (Appraisal of Guidelines for Research & Evaluation, the AGREE Collaboration, 2001) format, as recommended by the K-GINE (Table 4).

Table 4. The Korean Guideline Instrument for Evaluation (K-GINE)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Appraisal items</th>
<th>NICE-SCE</th>
<th>EFN</th>
<th>AAN</th>
<th>SIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose of the guideline</td>
<td>The overall objective(s) of the guideline is(are) described. The patient or population group(s) to whom the guideline is meant to apply is(are) described. The target users of the guideline are described.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The key question(s) covered by the guideline is(are) described. The entities in charge of guideline development are described. Detailed information on the development group members is provided.

Developing entities and stakeholders
Composition of the development group is interdisciplinary. The contents of the guideline have been peer-reviewed. The guideline is officially endorsed by relevant academic societies or other bodies.

Rigor of development
Systematic literature search has been performed. Systematic search of the local literature has been performed. The procedure of consensus building over recommendations is described. Recommendations are granted an evidence level or grade. The guideline is supported with tools for wide use.

Applicability and policy implications
Area(s) with limited evidence and the need for further research is(are) clarified. A procedure for guideline update is provided. Individuals or organizations funding the guideline development are specifically described. Subject-related conflicts of interest within the development group have been covered.

Ethical issues


Selection criteria included currency, content substantiability, consistency through evidence, interpretations, and recommendations, and regional characteristics. Along with quality appraisal of the guidelines, we also reviewed whether the retrieved guidelines were suitable for adaptation in view of the local healthcare environment. The process led to the selection of the 4 most prestigious and authoritative clinical practice guidelines for dementia, presented in Table 5.

Table 5. The Selected Source Guidelines for adaptation of the CPG for dementia

<table>
<thead>
<tr>
<th>Publisher(Authors)</th>
<th>Title</th>
<th>Booklet(Article)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 National Collaborating Centre for Mental Health</td>
<td>A NICE–SCIE Guideline on supporting people with dementia and their carers in health &amp; social care</td>
<td>Psychological Society &amp;Gaskell, 2007</td>
</tr>
</tbody>
</table>
Key questions needed to be addressed for adaptation were formulated based on the contents of the selected guidelines (Table 6). The questions were converted to proper problem definitions using the PICO method (P: patient, I: Intervention, C: Comparison, O: outcome), which formed the outlines of the new guideline.

Table 6. Key questions of CPG for dementia

<table>
<thead>
<tr>
<th>1</th>
<th>Overview of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Definition of dementia</td>
</tr>
<tr>
<td>1.1.1</td>
<td>What is(are) the definition(s) of dementia?</td>
</tr>
<tr>
<td>1.1.2</td>
<td>What are the medical models of dementia?</td>
</tr>
<tr>
<td>1.2</td>
<td>Epidemiology of dementia</td>
</tr>
<tr>
<td>1.2.1</td>
<td>What are the characteristics unique to dementia epidemiology studies?</td>
</tr>
<tr>
<td>1.2.2</td>
<td>What are the local prevalence and incidence of dementia?</td>
</tr>
<tr>
<td>1.2.3</td>
<td>What are the prevalence and incidence of dementia in other countries?</td>
</tr>
<tr>
<td>1.3</td>
<td>Etiology of dementia</td>
</tr>
<tr>
<td>1.3.1</td>
<td>What are the genetic factors contributing to dementia?</td>
</tr>
<tr>
<td>1.3.2</td>
<td>What are the environmental factors contributing to dementia?</td>
</tr>
<tr>
<td>1.4</td>
<td>Risk factors of dementia</td>
</tr>
<tr>
<td>1.4.1</td>
<td>What are the non-modifiable risk factors of dementia?</td>
</tr>
<tr>
<td>1.4.2</td>
<td>What are the modifiable risk factors of dementia?</td>
</tr>
<tr>
<td>1.4.3</td>
<td>Can history of severe mental illness, depression, or schizophrenia be the risk factors of dementia?</td>
</tr>
<tr>
<td>1.4.4</td>
<td>How is the level of intelligence associated with the risk for developing dementia?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Clinical Symptoms and Evaluation of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Clinical symptoms of dementia</td>
</tr>
<tr>
<td>2.1.1</td>
<td>What are the clinical presentations of dementia?</td>
</tr>
<tr>
<td>2.1.2</td>
<td>What are the courses and prognosis of dementia?</td>
</tr>
<tr>
<td>2.2</td>
<td>Diagnostic criteria for dementia</td>
</tr>
<tr>
<td>2.2.1</td>
<td>What are the currently available diagnostic criteria for dementia and their problems?</td>
</tr>
<tr>
<td>2.3</td>
<td>Evaluation of dementia</td>
</tr>
<tr>
<td>2.3.1</td>
<td>What are to be included in the medical history of patients with dementia?</td>
</tr>
<tr>
<td>2.3.2</td>
<td>What is the clinical significance of a semi-structured interview of caregivers?</td>
</tr>
<tr>
<td>2.3.3</td>
<td>How should physical and neurological examinations be performed in patients with dementia?</td>
</tr>
<tr>
<td>2.3.4</td>
<td>What co-morbidity should be evaluated in patients with dementia?</td>
</tr>
<tr>
<td>2.3.5</td>
<td>How should cognitive impairment be evaluated in dementia co-existing with depression?</td>
</tr>
<tr>
<td>2.3.6</td>
<td>How should cognitive impairment be evaluated in dementia co-existing with mental retardation?</td>
</tr>
<tr>
<td>2.4</td>
<td>Behavioral and psychological symptoms of dementia (BPSD)</td>
</tr>
<tr>
<td>2.4.1</td>
<td>What is the need for BPSD evaluation in patients with dementia?</td>
</tr>
<tr>
<td>2.4.2</td>
<td>What are the common BPSD in patients with dementia?</td>
</tr>
<tr>
<td>2.4.3</td>
<td>What are the impacts of co-morbidity on BPSD?</td>
</tr>
<tr>
<td>2.4.4</td>
<td>What tools are used for evaluation of BPSD?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.5</th>
<th>Activities of daily living (ADL) in dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5.1</td>
<td>What is the significance of ADL evaluation in patients with dementia?</td>
</tr>
<tr>
<td>2.5.2</td>
<td>What are the tools used for ADL evaluation in patients with dementia?</td>
</tr>
<tr>
<td>2.5.3</td>
<td>What is the diagnostic value of ADL evaluation in early detection of dementia?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Diagnostic Tests for Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Cognitive tests</td>
</tr>
<tr>
<td>3.1.1</td>
<td>What is the need for cognitive testing in patients with dementia?</td>
</tr>
</tbody>
</table>
What items should be included in the cognitive testing of patients with dementia?
What is the significance of cognitive testing as a screening test for dementia and what items can be included?
In what cases is comprehensive cognitive testing needed in patients with dementia?
What is the usefulness of a computerized cognitive test?
What is the role of cognitive testing in differential diagnosis of dementia?

### Laboratory tests
- What is/are the objective(s) of laboratory tests for diagnosis of dementia?
- What blood test items are needed in the diagnostic process of dementia?
- In what cases is the cerebrospinal fluid (CSF) test necessary in the diagnostic process of dementia?
- What is the usefulness of measuring Aβ42, phosphor-tau, and tau in CSF?
- In what cases is electroencephalography needed for diagnosis of dementia?
- In what cases is brain biopsy needed for diagnosis of dementia?
- In what cases is genetic testing needed for diagnosis of dementia?
- What are the biological markers of dementia?
- What are the laboratory test results predictive of the conversion of mild cognitive impairment (MCI) into dementia?

### Brain imaging tests
- What are the types of brain imaging used for diagnosis of dementia?
- How should the magnetic resonance image (MRI) protocol be structured for diagnosis of dementia?
- What are the indications for brain imaging for diagnosis of dementia?
- How is the cerebral atrophy manifested in the dementia-related disease?
- What is the implication of hippocampal atrophy in Alzheimer disease?
- What is the usefulness of SPECT (single photon emission computed tomography) in diagnosis of dementia?
- What is the diagnostic usefulness of positron emission tomography (PET) as a screening test for dementia?
- What is the diagnostic usefulness of amyloid PET for differential diagnosis of dementia?
- What is the usefulness of other functional brain imaging for diagnosis of dementia?

### Treatment of Dementia
1. **Basic principles of dementia treatment**
   - What are the basic principles of dementia treatment?
   - What are to be included in the guideline for periodic follow-up monitoring?

2. **Pharmacologic treatment of dementia**
   - What is/are the principle(s) of pharmacologic treatment of dementia?
   - What are the pharmacologic treatment options for cognitive symptoms of dementia?
     - What are the efficacy and effectiveness of cholinesterase inhibitors?
     - What are the efficacy and effectiveness of N-methyl D-aspartic receptor antagonists?
     - What are the efficacy and effectiveness of other drug treatments (gingko biloba, estrogen, antioxidants etc.)?
   - What are the pharmacologic treatment options for BPSD?
     - What are the efficacy and effectiveness of anti-depressants?
     - What are the efficacy and effectiveness of anxiolytics?
     - What are the efficacy and effectiveness of antipsychotics?
   - What are the side effects of pharmacologic treatments of dementia that require caution?

3. **Non-pharmacologic treatment of dementia**
   - What is/are the principle(s) of non-pharmacologic treatment of dementia?
   - What items should be evaluated for non-pharmacologic treatment of dementia?
   - What are the effectiveness of the individual and/or group cognitive stimulation programs?
   - How are the psychotherapy and behavior therapy for anxiety and depression performed in patients with dementia?
   - What are included in other non-pharmacological treatment of dementia?

4. **Treatment guideline by major causes of dementia**
   - What are to be included in the treatment guideline for Alzheimer disease?
   - What are to be included in the treatment guideline for vascular dementia?
   - What are to be included in the treatment guideline for other types of dementia such as diffuse Lewy bodies dementia (DLB), fronto temporal dementia, (FTD) etc?
   - What are to be included in the treatment guideline for MCI and vascular MCI?

5. **Other issues related to dementia treatment**
   - What are the BPSD that imply emergency?
   - What are the indications for institutionalization in patients with dementia?
   - What measures need to be taken in the last hours of life for patients with dementia?

### Prevention of Dementia
1. **Basic principles of dementia prevention**
   - What is(are) the basic principles of dementia prevention?
   - What are the major considerations in devising dementia prevention strategies?
   - The effects of dementia prevention therapy
5.2.1 What are the effects of controlling modifiable risk factors on prevention of dementia?
5.2.2 What are the effects of hormone replacement therapy, nonsteroidal anti-inflammatory drugs, and antioxidants on prevention of dementia?
5.2.3 What are the effects of depression treatment on prevention of dementia?
5.2.4 What are the effects of exercise, education, intellectual stimulation on prevention of dementia?

6 Early Detection of Dementia

6.1 What are the problems in early detection of dementia?
6.1.1 What is the usefulness of a dementia screening test for the general population?
6.1.2 How should subjective cognitive impairment be investigated?
6.1.3 What are the factors predictive of the progression from MCI to dementia?
6.1.4 What are the early clinical symptoms of major causes of dementia?
6.1.5 What are the early clinical symptoms of Alzheimer disease?
6.1.5.1 What are the early clinical symptoms of vascular dementia?
6.1.5.2 What are the early clinical symptoms of other types of dementia such as DLB, FTD, etc?

7 Socioeconomic Implications of Dementia

7.1 Human rights of patients with dementia
7.1.1 How should the human rights of patients with dementia be respected and sustained throughout the medical care?
7.1.2 What methods can be taken to prevent abuse and negligence toward patients with dementia?
7.1.3 What are to be included in the ethics involved in clinical research of dementia?
7.2 Legal issues
7.2.1 When and how should the diagnosis of dementia be disclosed to patients?
7.2.2 How can social consensus be built over the legal rights of dementia patients (such as rights to decision-making, execution of property rights, will-making, etc.)?
7.2.3 How should a decision-making committee formed for patients with dementia who are incapable of self-decision making?
7.3 Economic issues
7.3.1 How should the public nursing service be organized for patients with dementia and carers?
7.3.2 What is the size of the national cost incurred by dementia?
7.4 Human resources and facilities for dementia
7.4.1 How should the training and education for dementia patients and carers be implemented?
7.4.2 How should the healthcare professionals dedicated to dementia care be nurtured and evaluated?
7.4.3 What structures and functions of an individual residence environment are suitable for patients with dementia?
7.4.4 What should be included in the group residential environment (dementia hospitals, nursing homes, etc.) suitable for patients with dementia?
7.4.5 What items should be included in the evaluation of dementia-related facilities?

At the end of each chapter, recommendations were suggested with supporting evidence stratified as Level A, B, or C (Table 7, Brainin et al, 2004). For references, the 4 source guidelines and their original references mentioned were all quoted, conforming to the general paper writing principle. Efforts were made to include as much local dementia data as possible in an attempt to avoid a uniform acceptance or simple translation of foreign guidelines and to devise a practical guideline that best meets the local healthcare needs.

Table 7. Evidence classification scheme of the CPG for dementia

| Class I: | A prospective study in a broad spectrum of persons with the suspected condition, using a gold standard for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy |
| Class II: | A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by gold standard) compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy |
| Class III: | Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation |
| Class IV: | Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls) |

Rating of recommendations

| Level A | rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies |
Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies

3. Finalization phase

The final step of guideline development is to perform an external evaluation of a completed guideline and obtain endorsement from involved stakeholders. The preliminary CPG for dementia was sent to 33 clinical research centers for dementia nationwide for internal assessment before external evaluation. Based on the input, the development group made necessary modifications, and the revised version went through a public hearing jointly organized by National Clinical Research Coordination Center (NCRC) established by the Korean Centers for Disease Control. All dementia-related academic societies including the Korean Neuropsychiatric Association, the Korean Neurological Association, the Korean Association for Geriatric Psychiatry, and the Korean Dementia Association participated in this hearing. Their confirmation further improved the objectiveness of the CPG for dementia, and the final version became available after internal review of input gathered from the hearing and making necessary modifications. The procedural excellence, which guaranteed a broad participation and consensus by all members of the dementia related societies, led to the generation of a quality guideline with a wide practical value.

Scope of CPG for dementia

CPG for dementia targets not only the psychiatrists and neurologists at secondary or tertiary hospitals who provide professional clinical care for patients with dementia, but also internists, family physicians, and other primary physicians involved in prevention and early diagnosis of dementia. While it mainly covers Alzheimer’s disease (AD) and vascular dementia (VaD); the two most common causes of dementia, CPG for dementia also includes mild cognitive impairment (MCI) and vascular MCI, which are currently thought to be the preclinical period of AD or VaD, respectively, with emphasis on early diagnosis. The guideline focuses on diagnosis and evaluation areas of clinical practice, and the contents are divided as follows; 1. The etiologies and epidemiology of dementia, 2. The diagnostic criteria and evaluation of dementia, 3. The neuropsychological evaluation of dementia, 4. The behavioral and psychological symptoms of dementia (BPSD) and activities of daily living (ADL) abilities, 5. The laboratory tests for the diagnosis of dementia, and 6. The brain imaging for the diagnosis of dementia. With its emphasis on practicality and usefulness, CPG for dementia contains all domestically available tests for the neuropsychological evaluation, ADL assessment, lab tests, and brain imaging.

Future tasks

CPG for dementia leaves behind 3 main tasks: implementation, supplementation, and currency maintenance. First, it is important to make sure that the new guideline is used in as many hospitals as
possible. To this end, the guideline has been made accessible online at the web page of CREDOS (http://www.crcc.or.kr) and NCRC (http://ncrc.cdc.go.kr). It was also published in the Journal of the Korean Medical Association(KMA) (J Korean Med Assoc 2011; 54) in the form of a review article and also was made available on the web page of KMA (http://www.jkma.org). With advancements in communication technology, the abbreviated form of CPG for dementia can be available as the smart phone application or E-book linked in the web page of CREDOS (http://www.crcc.or.kr). CPG for dementia will also be made into booklets and CDs and distributed to public health centers and their branches nationwide. Symposiums on CPG for dementia utilization are planned for community sentinel hospitals. True to any clinical practice guidelines, underutilization greatly damages the rationale for the existence of a guideline. Second, any information in CPG for dementia whose evidence is weak or controversial should be supplemented with further evidence. If necessary, such evidence should come from clinical trials. Third, since CPG for dementia sourced foreign dementia guidelines published before 2007 for adaptation, modification might be needed to keep it up to date with relevant guidelines published thereafter. While focusing on the diagnosis and evaluation of the clinically common causes of dementia, CPG for dementia left out treatment and management. They, however, will be covered in supplements in the future. In fact, CREDOS plans to develop ‘CPG for dementia part II: Treatment and Management’ (Table 8). Other causes of dementia left out in the present CPG for dementia should also be included in the future.

Table 8. CPG for dementia - Part II: Treatment and Management

<table>
<thead>
<tr>
<th>Phase</th>
<th>Module</th>
<th>Step</th>
<th>Tasks</th>
<th>Outputs</th>
<th>Developmental details</th>
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</thead>
<tbody>
<tr>
<td>Set-up</td>
<td>1. Preparation</td>
<td>1</td>
<td>Formation of the steering committee</td>
<td>The CPG for dementia – part II: treatment &amp; management steering committee</td>
<td>Maintaining the earlier CPG for dementia steering committee with multi-disciplinary inputs from clinicians (neurologists and psychiatrists), search experts methodology experts, and other stakeholders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Subject determination</td>
<td>CPG for dementia – part II: treatment &amp; management subjects</td>
<td>Alzheimer disease (AD), vascular dementia (VaD), mild cognitive impairment (MCI), vascular cognitive impairment (VCI)</td>
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<td></td>
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<td>3</td>
<td>Adaptation feasibility review</td>
<td>A list of the related guidelines</td>
<td>The earlier CPG for dementia list of guidelines was furnished with later publications (from the American Psychiatric Association and the third Canadian Consensus Conference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Formation of the working committee</td>
<td>The CPG for dementia – part II: treatment &amp; management working committee</td>
<td>Organizing CPG for dementia-part II treatment &amp; management working committee</td>
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<tr>
<td></td>
<td></td>
<td>5</td>
<td>Disclosure of conflicts of interest</td>
<td>Disclosure statement</td>
<td>Maintaining the earlier CPG for dementia disclosure statement</td>
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<td></td>
<td>Planning task execution</td>
<td>Determination of endorsement affiliation</td>
<td>A list of the endorsement bodies</td>
<td>The Korean Association for Geriatric Psychiatry, the Korean Dementia Association, the Korean Neurological Association, and the Korean Neuropsychiatric Association</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Determination of authors</td>
<td>Determination of authors for each chapter</td>
<td>Authors were chosen from the CPG for dementia – part II treatment &amp; management working committee</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dissemination and implementation strategies</td>
<td></td>
<td>The implementation strategies</td>
<td>CPG for dementia – part II treatment &amp; management was plan to be published as a review article in the Journal of the Korean Medical Association (KMA), and linked to the the CREDOS, KGC and KMA websites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Documentation of adaptation plans</td>
<td></td>
<td>The CPG for dementia</td>
<td>Scope: treatment of AD, VaD, MCI, and VCI</td>
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<td>A list of the working members: dementia clinicians</td>
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<td>Adaptation</td>
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<tr>
<td><strong>2. Scope and goals</strong></td>
<td>7</td>
<td><strong>Scope and key questions</strong></td>
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<td>Key questions</td>
<td>A list of the key questions</td>
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<td><strong>3. Search and screening of source guidelines</strong></td>
<td>8</td>
<td><strong>Search for the source guidelines and references</strong></td>
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</tr>
<tr>
<td>A list of excluded guidelines and reasons for exclusion</td>
<td>Existing guidelines for treatment of dementia and relevant literature were searched; when they failed to provide answers for key questions, the scope of questions was modified or the latest systematic review was searched.</td>
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<tr>
<td><strong>9. Screening of the retrieved guidelines</strong></td>
<td>9</td>
<td><strong>Screening of the retrieved guidelines</strong></td>
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<td>A list of excluded guidelines from screening</td>
<td>Selection was made among the retrieved guidelines</td>
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<td><strong>10. Narrowing the guideline pool</strong></td>
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<td><strong>Narrowing the guideline pool</strong></td>
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<td>A list of further excluded guidelines</td>
<td>Further selection from the screened guidelines based on the key questions, the year of publication, language, development group, subjects, and scope</td>
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<tr>
<td><strong>11. Guideline quality assessment</strong></td>
<td>11</td>
<td><strong>Guideline quality assessment</strong></td>
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<tr>
<td>AGREE evaluation of the selected guidelines for adaptation</td>
<td>Evaluation of the further selected guidelines based on the scope and goals, participation of stakeholders, rigor of development, clarity and expression, applicability, and editorial independence</td>
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<tr>
<td><strong>12. Guideline currency assessment</strong></td>
<td>12</td>
<td><strong>Guideline currency assessment</strong></td>
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<tr>
<td>A summary table for the currency of the key guidelines</td>
<td>Evaluation of the key guidelines based on the currency summary table</td>
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<td><strong>4. Source guideline assessment</strong></td>
<td>13</td>
<td><strong>Guideline contents assessment</strong></td>
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<tr>
<td>A table for comparison of recommendations</td>
<td>To be omitted</td>
<td></td>
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</tr>
<tr>
<td>A summary table for the recommendations of the key guidelines</td>
<td>Evaluation of validity of evidence, consistency of evidence and recommendations, and risk of bias</td>
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<tr>
<td>A summary table for the consistency through evidence, interpretations, and recommendations</td>
<td>Evaluation of the acceptability and applicability of the recommendations</td>
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<td><strong>5. Review of assessment</strong></td>
<td>15</td>
<td><strong>Assessment of acceptability and applicability of recommendations</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>6. Decision and selection</strong></td>
<td>16</td>
<td><strong>Review of assessment</strong></td>
<td></td>
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<td><strong>7. Draft guideline preparation</strong></td>
<td>17</td>
<td><strong>Selection and modification of recommendations</strong></td>
<td></td>
<td></td>
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<tr>
<td>The draft recommendations of the CPG for dementia – part II treatment &amp; management</td>
<td>Certain recommendations from the key guidelines were modified.</td>
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<td><strong>8. Draft preparation</strong></td>
<td>18</td>
<td><strong>Draft preparation</strong></td>
<td></td>
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</tr>
<tr>
<td>Preparation was based on the guideline writing principles and the recommendation modification report form</td>
<td>Each subject of the draft CPG for dementia – part II</td>
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</tr>
<tr>
<td>External review and endorsement</td>
<td>Request of the official endorsement</td>
<td>Advisory input from the original source guideline authors</td>
<td>Sorting of the literature and references</td>
<td>Plans for future review and update</td>
<td>Writing of The final guideline</td>
</tr>
<tr>
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</tr>
<tr>
<td>Stakeholder opinion gathering, and target user research</td>
<td>A public hearing on the 'CPG for dementia – part II treatment &amp; management'</td>
<td>To be omitted</td>
<td>The CPG for dementia – part II treatment &amp; management revision plan</td>
<td>Development of a CPG for other causes of dementia</td>
<td>The CPG for dementia – part II treatment &amp; management full text</td>
</tr>
<tr>
<td>Measures</td>
<td>A public hearing was jointly organized with NCRC.</td>
<td>Accreditation by dementia-related academic entities (the Korean Neuropsychiatric Association, the Korean Neurological Association, the Korean Dementia Association, the Korean Association for Geriatric Psychiatry)</td>
<td></td>
<td>Evidence should be established through clinical trials where the existing evidence is absent or weak. Dissemination should be emphasized for a wide use at the place of patient care.</td>
<td></td>
</tr>
</tbody>
</table>

### Support for CPG for dementia development

CPG for dementia has been developed by CREDOS with support from the Korean Ministry of Health and Welfare as part of its Healthcare Technology Promotion Project (A050079). Led by Principal Investigator Duk L. Na, MD (Department of Neurology, Sungkyunkwan University, School of Medicine, at Samsung Medical Center Seoul, Korea) CREDOS undertakes 5 subprojects. CPG for dementia is an outcome of the extensive efforts to develop a clinical practice guideline and education programs tailored to the Koreans. All members of the steering committee and the working committee who participated in the research for CPG for dementia development, have not received any other support except for the above mentioned Korean government support.

### Endorsement of CPG for dementia

CPG for dementia has been endorsed through a hearing titled the ‘Clinical Practice Guideline for Dementia and Recommendations for Cognitive Health in the Elderly’ held September 19 2009. The accrediting academic societies include the followings (shown in the alphabetical order).

- The Korean Association for Geriatric Psychiatry
- The Korean Dementia Association
- The Korean Neurological Association
- The Korean Neuropsychiatric Association
The CPG for dementia development group

An expert group was formed for development of CPG for dementia. The composition of members was multidisciplinary, including psychiatrists, neurologists, guideline developmental experts, and search experts. To improve efficiency of adaptation, the group was structured to include a chairman, principal members, operating members, advisory members, working members, and assistant administrators (Table 9). The principal members, advisory members, and operating members built consensus by continuously exchanging opinions and fine-tuning differing views throughout the adaptation process (Table 2).

Table 9. The CPG for dementia development group

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Organization</th>
<th>Position</th>
<th>Name</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman</td>
<td>Seo-Hhee</td>
<td>Department of Neurology, Konkuk University</td>
<td>Operating</td>
<td>Sang Won</td>
<td>Department of Neurology, Sungkyunkwan University</td>
</tr>
<tr>
<td>Principal</td>
<td>Han</td>
<td>Department of Neurology, Sungkyunkwan University</td>
<td>members</td>
<td>Chang Hyung</td>
<td>Department of Psychiatry, Ajou University</td>
</tr>
<tr>
<td>members</td>
<td>Duk L.Na</td>
<td>Department of Psychiatry, Sungkyunkwan University</td>
<td></td>
<td>Hong</td>
<td>Department of Neurology, Chung-Ang University</td>
</tr>
<tr>
<td>Sung Yoon</td>
<td>Kim</td>
<td>Ulsan University</td>
<td>Working</td>
<td>Yung Chul</td>
<td>Department of Neurology, Soochunhyang University</td>
</tr>
<tr>
<td>Doh Kwan</td>
<td>Department of Psychiatry, Sungkyunkwan University</td>
<td></td>
<td></td>
<td>Yoon</td>
<td>Department of Psychiatry, Seoul National University</td>
</tr>
<tr>
<td>Jae-Hong</td>
<td>Department of Neurology, Ulsan University</td>
<td></td>
<td></td>
<td>Shin-Kyum</td>
<td>Department of Psychiatry, Dongguk University</td>
</tr>
<tr>
<td>SangYun</td>
<td>Department of Neurology, Seoul National University</td>
<td></td>
<td>Working</td>
<td>Jun-Young</td>
<td>Department of Psychiatry, Gachon University Medicine &amp; Science</td>
</tr>
<tr>
<td>Byeong Kil</td>
<td>Department of Psychiatry, Hallym University</td>
<td></td>
<td></td>
<td>Lee</td>
<td>Department of Neurology, School of Public Health &amp; Medicine</td>
</tr>
<tr>
<td>Hae-Kwan</td>
<td>Department of Social and Preventive Medicine, Sungkyunkwan University</td>
<td></td>
<td></td>
<td>Joon Hyun</td>
<td>Department of Neurology, Konkuk University</td>
</tr>
<tr>
<td>Cheong</td>
<td>Seoul National University</td>
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<td>Shin</td>
<td>Department of Neurology, Hallym University</td>
</tr>
<tr>
<td>Advisory</td>
<td>Soo Young</td>
<td>Department of Family Medicine, Hallym University</td>
<td>Working</td>
<td>Yung Min</td>
<td>Department of Psychiatry, Busan National University</td>
</tr>
<tr>
<td>members</td>
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<td>Hallym University</td>
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<td>Lee</td>
<td>Department of Neurology, Busan National University</td>
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<tr>
<td>Hye Min</td>
<td>Samsung Medical Information &amp; Media Center</td>
<td></td>
<td>Assistant</td>
<td>Bon D. Ku</td>
<td>Department of Neurology, Kwandong University</td>
</tr>
<tr>
<td>Cho</td>
<td></td>
<td></td>
<td>administrators</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments on CPG for dementia utilization by the development group

A clinical practice guideline is aimed at improving physician’s decision-making in the general clinical setting. The CPG for dementia, developed through the ADAPTE method, is the first guideline in Korea accredited by relevant stakeholders. However it is not intended to uniformly define diverse dementia-related clinical situations or to limit any clinical practice involved in dementia care. Indeed, the role of CPG for dementia is to provide useful information, not absolute standards, for care of patients with dementia. It should never be used to limit the clinical practice for the care of patients with dementia by healthcare professionals, nor should it be used for judgment for adequacy of specific clinical practice related to the care of dementia by the Health Insurance & Review Assessment Service. It should also not serve as a basis for legal judgment of any specific clinical practice related to dementia, since in the actual clinical setting, the experience and judgment of a physician often outweighs a standardized guideline.
References


Chapter 1. The Etiology and Epidemiology of Dementia

A. Definition of dementia

1. Definition of dementia

Dementia is defined as an acquired brain disorder characterized by memory impairment with one or more of disabilities including aphasia, apraxia, agnosia, and disturbance in executive functioning that is serious enough to cause significant impairment in social and occupational functioning (Diagnostic and Statistical Manual of Mental Disorders; DSM-IV American Psychiatry Association, 1994). According to the International Classification of Diseases (ICD-10) by the World Health Organization (WHO), dementia is a syndrome due to diseases of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. The cognitive impairment severe enough to interfere with personal activities of daily living should last at least 6 months without clouding of consciousness (WHO, 1992). Put together, dementia is a state where multiple cognitive deficits caused by acquired brain disorder result in difficulties with daily activities or social life (Mendez et al, 2003). Multiple cognitive deficits is defined here as presence of either one or more cognitive dysfunction with memory impairment or, if memory impairment is absent, 3 or more of the following cognitive dysfunctions; language disturbance, visuospatial agnosia, changes in personality and mood, and disturbance in frontal executive function (Mendez et al, 2003).

2. Medical models of dementia

(1) Presenile versus senile dementia

Early-onset or pre-senile dementia refers to dementia where the symptoms first appear before the age of 65. In the late-onset or senile dementia, dementia symptoms are seen at the age of 65 or later. They differ in causes, clinical symptoms, and disease courses. The classification of dementia by age is not only clinically useful, but allows a special management system for those with early-onset dementia (Harvey et al, 2003).

(2) Mixed dementia

Autopsy findings of patients with Alzheimer’s disease (AD) showed that 60-90% of them also had various other cerebrovascular lesions. Those with cerebral lesions had severe early dementia symptoms with rapid progression compared with other AD patients with similar pathological findings without cerebral lesions, suggesting that vascular lesions are a major factor for the development of symptoms of AD. In the autopsy of patients clinically diagnosed with vascular dementia (VaD), one third of them showed pathological findings of AD. The evidence implies that the two types of dementia overlap in many cases (Snowdon et al, 1997). Not only VaD, but AD is often mixed with dementia with Lewy bodies (DLB) where the pathological findings of the two diseases are simultaneously present, each with discreet clinical symptoms (Snowdon et al, 1997). One can say that mixed dementia in which different causes co-exist is found in a considerable portion of dementia patients, particularly in the so-called oldest-old population.
Indeed, mixed dementia was the most common cause of dementia in one large-scale neuropathological study conducted in Britain (MRC/CFAS 2001).

(3) Mild cognitive impairment and vascular mild cognitive impairment

Mild cognitive impairment (MCI) is defined as decline in cognitive function not accompanied by disturbance in activities of daily living (ADL) (Petersen et al, 1999). MCI is a pre-clinical state of dementia, an intermediate between normal aging and dementia. Follow-up of patients with MCI revealed that each year 10-15% of them progress to dementia, far higher than the yearly dementia incidence of 1-2% in the healthy elderly population aged ≥65 (Petersen et al, 2001). The diagnostic criteria for MCI include (1) presence of complaints about cognitive decline by patients or care-givers (2) impaired cognitive function for age and education, and (3) Preserved ADL. Despite the criteria, there is no consensus over how much impairment from normal cognitive function should make diagnosis of cognitive impairment and what neuropsychological tools should be used, rendering determination of MCI a subjective discretion of a clinical physician. By the currently available standard, cognitive impairment is defined by a test performance of more than 1.5 SD below the age- and education-matched norms (Petersen et al, 1999, 2001).

MCI is classified as amnestic-or non-amnestic MCI; amnestic MCI where memory loss is the predominant symptom, and non-amnestic MCI with impairments in the non-memory cognitive domains. By the number of affected domains, MCI is also classified as single- or multi-domain MCI. Patients with amnestic MCI are at high risk of progressing to dementia, particularly to AD (10-15% per year) (Bischkopf et al, 2002). Vascular MCI is a relatively recent concept used to indicate a prodromal state of VaD. Like in MCI, about half of the patients with vascular MCI were shown to progress to dementia over a 5-year follow-up period, spelling the need for proper treatment interventions aimed at prevention (Wentzel et al, 2001). MCI is a useful concept for the classification of the patients showing various stages of cognitive decline. It is also useful in identifying the patient group in need of early intervention in the form of disease modifying therapy (Petersen et al, 2005).

B. Causes and impacts of dementia

1. Types of dementia

Dementia is not a single disease, but rather a syndrome caused by various illnesses that affects brain function. About 70 causes of dementia have been reported (Katzman et al, 1993). By clinical course, dementia is classified into progressive (degenerative, irreversible), preventable, treatable, and other dementia.

The most common cause of dementia is AD, accounting for 60-70% of all cases of dementia, followed by VaD representing about 30%. While VaD is known to be caused by vascular injuries including ischemia, infarction and hemorrhage, differential diagnosis between AD and VaD is not easy in the clinical setting. Brain imaging might provide important clues for judgment, but ischemic lesions are often found in AD while pathological findings of AD are commonly observed in VaD. It is not unusual to encounter co-
existence of both pathological findings (Snowdon et al, 1997). Since the disease course of AD is of a continuously progressive nature, it is classified as progressive (degenerative, irreversible) dementia. On the other hand, VaD is a prototype of preventable dementia since a certain degree of improvement in symptoms can be expected if additional cerebrovascular events are prevented with proper medical intervention. AD and VaD together make up about 80% of the total causes of dementia.

Of progressive (degenerative, irreversible) dementia, the second common type after AD is DLB, accounting for about 20% of progressive dementia and 8% of total dementia (Mendez et al, 2003). DLB shares characteristics with both Parkinsonism and dementia. About 30-70% of patients with Parkinson's disease develop dementia symptoms as the disease course is prolonged (Aarsland et al, 2003). At the present, the association between Parkinson's disease with dementia (PDD) and DLB is determined by the time frame in which the Parkinson symptoms appear relative to the cognitive symptoms. Diagnosis of DLB is highly likely if cognitive symptoms precede the Parkinson symptoms or appear within 12 months of the onset of Parkinson symptoms (McKeith et al, 1996). Other cases are considered PDD, mainly for the sake of convenience. Frontotemporal dementia (FTD) is the third most common progressive (degenerative, irreversible) dementia, accounting for about 6% of total dementia. In this type of dementia, abnormal behaviors, personality changes, and language disturbance precede memory impairment. The average age of onset is lower than in AD (Neary et al, 1998). FTD is further classified by the pattern in which the frontal and temporal lobes are affected; behavioral variant FTD whose hallmark symptoms are personality changes and behavioral disorder, semantic dementia mainly with progressive language disturbance, and progressive nonfluent aphasia (Grossman, 2002). Other causes of progressive (degenerative, irreversible) dementia include alcohol, human immunodeficiency virus, Huntington's disease, and prions (Creutzfeldt-Jacob disease).

One of the most important considerations in evaluating patients with dementia is to identify a treatable cause. Proper treatment of a cause might help patients with impaired cognition/dementia revert to the normal, prior-to-onset state. Typical causes of a treatable or reversible dementia include psychiatric disorder (depression, etc.), space-occupying lesions (chronic subdural hematoma, brain tumor, brain abscess etc.), drugs or toxins, endocrine disorder (vitamin B12 deficiency, folate deficiency, thyroid disease, etc.), hydrocephalus, and infection (neurosyphilis, etc.). The association of depression with dementia is particularly important. While depression could be an underlying cause of dementia, a number of patients with dementia, particularly AD, show symptoms of depression in the early stage of the disease. In these cases, treatment should target not only AD, but depression. The reversible types account for approximately 5% of total dementia. While many of the treatable physical conditions mentioned above are quite common, they are mostly diagnosed and treated for other symptoms before progressing enough to cause dementia in the clinical practice, and seemingly accounts for a negligible portion of total dementia. The treatable causes of dementia, however, should be taken into consideration in patient evaluation, since their early diagnosis and proper medical intervention lead to successful treatment of dementia symptoms and even reversal to the normal (NICE-SCIE, 2007).
2. Physical and social impacts of dementia

Patients with dementia are at an increased risk of developing other health problems. They are prone to delirium induced by medical conditions or drugs. Those with VaD or DLB tend to show motor symptoms similar to stroke or Parkinson’s disease. Over the disease course, progressive (degenerative, irreversible) dementia such as AD, DLB, and FTD often presents non-specific neurological symptoms such as sweating, flush, and dizziness caused by autonomic degeneration. Reduced exercise, poor personal hygiene, and poor drug compliance make patients with dementia vulnerable to other diseases. In particular, malnutrition and weight loss worsen along the course of disease, and are pointed out as the major cause of complications and increased mortality in dementia patients. The care-givers, particularly to the advanced dementia, need to pay a close attention to the nutritional state and hygiene of the patients (Watson et al, 2002).

Treatment of dementia involves not only medical but social aspects as well. As a large part of patient care falls on the shoulders of family members, they suffer emotional, physical, and financial difficulties, which require a broad social support. Research has shown that mental illness such as depression is found in about 30% of the care-givers of dementia patients (Donaldson et al, 1998). Despite the efforts to enhance awareness of dementia over the past few years, dementia remains highly negatively perceived and feared as a disease that not only distresses patients but causes a huge social and economic burden for care-givers (Kang et al, 2005; NICE-SCIE, 2007).

C. Epidemiology of dementia

1. Significance of dementia in an aged society

The number of patients with dementia increase with age, almost doubling every 5 years after the age of 65 (John et al 1987). Korea became an aging society in which the elderly population aged ≥65 exceeded 7% of the total national population in 2000. If it grows at the current rate, the elderly population will reach 14.3% by 2018, making Korea an aged society (National Statistics Office, 2003). Accordingly, the number of patients with dementia is predicted to rise from about 400,000 to 700,000 by 2020, causing a huge socioeconomic problem (Kang et al, 2005). The rapid expansion of dementia population and subsequent social burden has become one of the most serous healthcare issues in Korea. Understanding the epidemiological factors regarding dementia is imperative to devise social consensus aimed at prevention and management of the dementia.

2. Characteristics of the dementia epidemiology survey

The most common causes of dementia are AD and VaD, constituting about 80% of total dementia. However, surveys have shown varying results depending on when, where, and on whom they were conducted. The inconsistence is attributable to the difference in gender and age composition of the subjects (Rocca et al, 1991), the inclusion criteria, the dementia screening criteria, the population size, the methods and procedures for patient identification (Henderson et al, 1987), and inclusion and/or exclusion of the facility resident patients. And the definition or diagnostic criteria of dementia (Kay et al,
number of patients with AD was estimated at about 5% in those aged \( \geq 65 \) ranged 2.2-8.4% worldwide, with Europe showing a slightly higher rate (5.2-8.4%) compared with Asia (2.2-6.8%). They also said that mild cases accounted for about 50-65% of total dementia, with the prevalence of AD in the elderly (age \( \geq 65 \)) ranging 1.6-15.3%. The risk of developing AD rapidly increased with age, and its prevalence was more than twice that of VaD (NICE-SCIE, 2007).

According to the prevalence studies in the US, approximately 2 million Americans were diagnosed with AD in 1997, and the total number of patients with AD was estimated at about 4.5 million (Katzman et al, 1999). The number is predicted to reach 14 million by 2050, with 250,000 newly diagnosed patients added each year (National Institute on Aging, 2003). In one study conducted in Boston, US, that included patients with only a mild decline in ADL, the yearly AD incidence was about 0.6% in the age group of 60-65 (Hebert et al, 1995). In the Framingham study including patients with moderate to severe dementia, the incidence was reported at 0.07% (Bachman et al, 1993). To put together multiple epidemiological studies in the US, the overall incidence of dementia by age was 0.33% (age 65-69), 0.84% (age 70-74), 1.82% (age 75-79), 3.36% (age 80-84), and 5.33% (age 85-89). The incidence of AD showed a similar pattern, with 0.19% (age 65-69), 0.51% (age 70-74), 1.17% (age 75-59), 2.31% (age 80-84), and 3.86% (age 85-89). The prevalence of dementia or AD was 14 times higher in those aged \( \geq 85 \) than in the age group of 65-69 (Gao et al, 1998). In the US studies on VaD, not only those with authentic cerebrovascular pathologies, but AD patients were included, in which VaD represented 10-30% of total dementia (Roman et al, 1993).

In Europe where about 5 million people are subject to dementia-related physical, emotional, and social sufferings, dementia is perceived as a huge social burden (Andlin-Sobocki et al, 2005, Olesen et al, 2003). According to the Medical Research Council-funded Cognitive Function and Aging Study (MRC-CFAS) in Britain, the original estimation of 550,000 dementia patients in 1998 increased to 700,000 as the research went by (MRC/CFAS, 1998; Alzheimer’s society, 2000). In a large-scale European study on dementia epidemiology, the prevalence of dementia by age group was shown at 1% (age 60-65), 13% (age 80-85), and 32% (age 90-95) (Hofman et al, 1991). It also turned out 5% in those aged \( \geq 65 \) and 20% in those aged \( \geq 80 \). In another study, the prevalence was 1-3% per 1,000 (age 65-70) which increased with age to 13% (age 80-85) and to 32% (age 90-95) (Fratiglioni et al, 1991). The prevalence of VaD in Europe was 0.12% in men and 0.03% in women (per 1,000, age 65-70). Being slightly higher in women in that age group, the rate leveled between gender with age at 0.6% (age 85-90) (Lobo et al, 2000). The time taken for the prevalence of dementia to double past the age of 65 was 4.5 years in AD and 5.3 years in VaD.
(Jorm & Jolley, 1998). Though evidence on the prevalence of DLB is not yet definitive, a recent British study reported it at about 11% of total dementia (Steven et al, 2002). In a European study involving younger patients with dementia, the prevalence was 54 per 100,000 (age 30-64), with the actual number of the younger patients estimated at about 14,000 (Harvey et al, 2003).

In a Japanese study on the prevalence of dementia, the number of dementia patients, reported at about 1 million in 1990, was predicted to rise to 2.62 millions by 2015 (The Japanese Ministry of Health and Welfare, 1994). While VaD had been reported more prevalent than AD in the past Asian studies (Yokoi et al, 1983; Shibayama et al, 1986), a recent report showed otherwise. Contrary to the results in studies published before 1994, Ogura et al (1995) argued that the overall dementia prevalence was 6.7%, with the prevalence of AD 1.5 times that of VaD (Ogura et al, 1995). Nonetheless, an in-depth Japanese analysis of the brain imagings and autopsy results in 2001 showed that VaD was 1.3 times more prevalent than AD, suggesting that VaD continues to outweigh AD in clinical significance in Asia (Ikeda et al, 2001). Meanwhile, in studies conducted in Shanghai (Zhang et al, 1990) and Hong Kong (Chiu et al, 1998), the prevalence of dementia in the elderly aged ≥65 was 4.6% and 6.1%, respectively, with AD found in 65% of the total dementia patients in both studies.

4. Korean studies on the incidence and prevalence of dementia

The prevalence of dementia has been investigated in several surveys in Korea since 1990. In the local epidemiological surveys (Park et al, 1994; Woo et al, 1998; Cho et al, 1998; Kim et al, 1999; Seo et al, 2000; Lee et al, 2002; Kim et al, 2003), the prevalence of dementia in those aged ≥65 ranged 6.8-12.8%. The Korean Ministry of Health and Welfare recently conducted for the first time a dementia prevalence survey at a national level and reported that as of 2008, dementia affected 8.4% (420,000) of the elderly population aged 65≥, while 25% suffer MCI (Korean Ministry of Health and Welfare, 2009). Compared with the results from other countries, the prevalence of dementia here was shown higher and ranged wider. Estimations of the number of dementia patients also varies, but it is predicted to reach 920,000 by 2020, 1.09 millions by 2030, and 1.3 to 2.5 millions by 2050 (Seo, 2000; Kang et al, 2005). The most recent estimation was over 1 millions by 2027 (Korean Ministry of Health and Welfare, 2009).

The higher incidence of dementia in Korea compared with other countries is attributable to the exclusion of a large number of facility resident patients seen in Japan or Western countries. In Korea, where nursing facilities for dementia patients are in short supply, more patients have been seemingly included in the prevalence surveys. Another factor might be the far lower education level of the Korean elderly population compared with their overseas counterparts (Kim DH, 2002), given the report that dementia is more common in those with lower education levels (Katzman, 1993).

In most Korean prevalence studies (Park et al, 1994; Woo et al, 1998; Seo et al, 2000; Lee et al, 2002), AD was shown almost twice more prevalent than VaD, though an opposite result was reported in one study (Kim et al, 1999). Gender distribution of the prevalence of VaD also varied among researchers. While some (Woo et al, 1998; Seo et al, 2000) observed a higher prevalence of VaD in men than in women, others reported an opposite gender pattern (Kim et al, 1999; Lee et al, 2002). Though AD was
recently reported as more prevalent than VaD in Korea (AD 71%, vascular dementia 24%, and others 5%), the prevalence of VaD was still relatively higher here compared with other countries (Korean Ministry of Health and Welfare, 2009).

The local prevalence of dementia was higher in women than in men in most studies. The pattern becomes more evident with increasing age, which is largely attributable to the sharp rise of AD in older women aged ≥80. In general, AD is more common in women, while VaD is more common in men in Korea. One consideration might be that the particularly high AD prevalence in women aged ≥80 is due to the high rate of illiteracy and lack of education in that population group, since the prevalence of dementia tends to go up in those with poor education (Seo et al, 2000; Kim et al, 2003; Korean Ministry of Health and Welfare, 2009). A recent national epidemiological study by the Korean Ministry of Health and Welfare showed that very mild dementia and mild dementia accounted for 70% of total dementia, underlining the significance of early detection and treatment (Korean Ministry of Health and Welfare, 2009).

Here is a summary of the epidemiological characteristics of dementia in Korea; 1) the prevalence of dementia is higher here than in other countries, 2) The prevalence of AD exceeds those of VaD, 3) dementia affects more women than men, and the trend becomes more evident with increasing age, which is attributable to the abrupt surge in the AD prevalence in older female population, 4) the prevalence of dementia is remarkably high in the poor education group, particularly in the illiterate, and 5) the rate of very mild or mild dementia is significantly high (Kim et al, 2002; Korean Ministry of Health and Welfare, 2009).

5. Progress and prognosis of dementia

The prevalence of dementia is expected to more than double within 30 to 50 years due to the expansion of the oldest old group (Wancata et al, 2003).

In a longitudinal study undertaken by the Mayo Clinic, the rate of conversion from MCI to AD was 12% yearly during the 4 year follow-up, and about 80% 6 years later (Petersen et al, 1999; 2001a,b). In a Canadian study, 14% of the MCI patients progressed to AD yearly over the 2-year follow-up, and 28% after 2 years (Tierney et al, 1996). According to a study by the Columbia University, USA, the conversion rate was 15% yearly over the 1.7 year follow-up, and 41% after 2.7 years (Devanand et al, 1997). In a study by the Harvard University, USA, including only patients with clinical dementia rating of 0.5, 6% of MCI progressed to AD each year over the 3-year follow-up, and 41% after 2.7 years (Daly et al, 2000). In a large-scale epidemiological study that followed up patients for 48 months in Seattle, USA, the rate of conversion from MCI to AD was 12% yearly, and 48% after 48 months (Bowen et al, 1997). In a study by the New York University, USA, using the global deterioration scale, the conversion rate was 25% yearly during the 2.2 year follow-up (Flicker et al. 1991). To put together the results, the rate of conversion from MCI to AD broadly ranged between 6-25% among studies. There is no local data available yet on the conversion rate.

The patients with MCI show a high rate of conversion to dementia compared with healthy controls. Though there is some controversy, MCI is surely considered as a risk factor of dementia. Close
monitoring of cognition and its decline is essential. Periodic healthcare services including cognitive testing aimed at early detection of dementia has proven its medical legitimacy (Petersen, 2001a,b). It is still unclear how different MCI subtypes affect the conversion to dementia. Also hardly known to the role a distinct pathological changes of in the cognitive decline in patients with mixed dementia such as AD with VaD, AD with DLB, etc.

6. Socioeconomic burdens of dementia

Studies from other countries have shown a wide variation in the estimated socioeconomic cost of dementia, ranging from 20 to 100 billion US dollars, most of which spent on patient care. The yearly cost of treatment and management of AD per patient appeared to be 1,547 to 79,822 US dollars. In the US, the average cost per AD patient for treatment and management of the disease was 40,000 dollars in 1998 (Brookmeyer et al, 1998). In Europe, dementia is the second most expensive disorder of the central nervous system ranked in terms of the amount of social burden, with about 55 billion Euros spent each year on the total dementia-related health care cost (Jonsson et al, 2005).

In Korea, the total official medical expenditure associated with dementia was 158.5 billion KRW in 2004. Of it, 66.7% was spent for women and 17.0% for those aged ≥85 who represented 66.1% and 12.6% of the total patients, respectively. Per patient monthly medical cost was approximately 1.86 million KRW, with 1.43 million KRW in patients in their late 60s and 2.10 million KRW in those aged ≥80. From the results, one can predict that the dementia-related medical cost will soar in Korea where the elderly population is growing fast. On average, a dementia patient spent 161 days admitted in hospital, with 6.20 million KRW incurred as the yearly cost. He or she made 9 outpatient visits per year, and the total cost was about 350,000 KRW. The estimation, however, was limited to the official counting. The yearly socioeconomic cost incurred by one dementia patient, both official and non-official, was estimated at 5.07 million KRW (direct cost). The indirect cost including the productivity loss of 990,000 KRW is an additional 2.91 million KRW. As a result, a dementia patient was shown to cost a total of 7.98 million KRW yearly (Kang et al, 2005). In Korea, the number of patients with dementia is predicted to rise to 700,000 by 2020 (the National Health Insurance Corporation, 2007), and the associated medical cost, even before adjustment for inflation, is estimated at 5.6 trillion KRW. According to the recent epidemiological survey by the Korean Ministry of Health and Welfare, per-person medical cost in patients with severe dementia was 8 times that in those with mild dementia, once again indicating the importance of early detection (Korean Ministry of Health and Welfare, 2009). A five-year delay in the onset of dementia cuts its prevalence in half (Jorn, 1998), and delay in the conversion from MCI to AD will lead to a considerable cost reduction (Petersen et al, 2001).

7. An ideal model for a dementia epidemiology survey

The unprecedented, super-fast aging of the Korean society warns of an exponential increase in dementia, a prototype senile disease, and a subsequent expansion of the socioeconomic burden. In many recent analytical epidemiology studies, dementia was deemed preventable to a great degree. In
order to establish comprehensive measures for prevention and management of dementia, an in-depth understanding of the local epidemiological features needs to precede (Korean Ministry of Health and Welfare, 2009).

Further study on the prevalence of dementia, using a random sampling and the standardized diagnostic criteria, is necessary. Also important is to build a large elderly cohort that allows a long-term follow-up and a systematic analysis of the related genetic and environmental factors.

D. Risk factors of dementia

The significance of risk factor studies lies in the fact that medical interventions targeting modifiable risk factors might possibly delay or prevent the onset of dementia and reduce the associated healthcare cost. While some risk factors are shared among many types of dementia, others are specific to a certain type (NICE-SCIE, 2007). Age and family history of dementia are particularly known to have a strong causal relationship with the onset of dementia (Fratiglioni, 1996). Age is probably the single most important factor associated with an increased risk of dementia. The prevalence and risk of onset has been shown to grow exponentially with age. That is, a 5-year delay in the age of onset would cut the prevalence of dementia in half (Jorm et al, 1987). Such tendency was observed in the incidence studies as well (Rocca et al, 1991). Important considerations in describing risk factors include if that particular factor is common with all types of dementia or limited to specific types, if it is modifiable or not, and how much preventive effects could be expected by controlling it (NICE-SCIE, 2007). The present CPG for dementia covers not only risk factors but protective factors, with the coverage focus on possible risk reduction achieved by active control.

1. Risk factor of dementia

(1) Non-modifiable risk factors

1) Age

Advanced age is the single greatest risk factor for AD, VaD, and DLB. However, FTD, Creutzfeldt-Jacob Disease (CJD), and Huntington’s disease are more common in the middle age (Harvey et al, 2003). Age is also important in that it provides time for the effects of other risk factors to appear, and is thus considered a typical non-modifiable risk factor.

2) Gender

The prevalence of AD is significantly higher in women than in men (Rocca et al, 1991). The difference is explained with a longer life expectancy, a rapid fall in the estrogen level after menopause, and a shorter education period in women. Nonetheless, the hormonal change or simple confounding factors such as life expectancy or poor education are not enough to explain the gender difference in the AD prevalence, which is almost twice as high in women (Geerlings et al, 2001). VaD is more prevalent in men, but the gap is narrowed with age and turned non-existent after the age of 90 (Lobo et al, 2000). VaD is more prevalent in men, but the gap is narrowed with age and turned non-existent after the age of 90 (Lobo et al, 2000).

3) Genetic factors

Down syndrome is a well-known disease causing dementia by the single chromosomal abnormality (Rabe et al, 1990). In patients with Down syndrome, the onset of AD is much earlier (usually in their 30s
to 40s) compared with those without Down syndrome (Visser et al, 1997; Tyrell et al, 2001). The risk of dementia increases in individuals with a family history of senile AD or VaD, but no chromosomal abnormalities have been reported.

Presenile AD with autosomal dominance inheritance accounts for 1% of total AD. Three genes are known to be involved in the pathogenesis; the amyloid precursor protein (APP) gene and presenilin 1 & 2 genes (Hardy, 1996; Schellenberg et al, 1991; Cruts et al, 1998). Autosomal dominant presenile AD usually developed before the age of 55 (Morris et al, 2005). However the other 99% of AD are thought to be caused by the complex interaction between genetics and environment.

The known susceptibility gene for senile AD is the apolipoprotein E (Apo E) ε4 allele. Though its role has not been clearly identified, Apo E is known to be involved in nerve sheath regeneration. There are three Apo E genetic polymorphism; Apo E ε2, ε3, and ε4 (Mann et al, 1996). The Apo E ε2 allele works as a protective factor against AD, but the ε4 allele is a risk factor that not only increases the risk of development but lowers the age of onset of AD (Strittmatter et al, 1993; Poirier et al, 1993; Cedazo-Minguez et al, 2001). In a recent prospective cohort study conducted in Canada, Lindsay et al (2002) reported that the risk of AD increases almost nine folds in the group with two ε4 alleles compared with those without it. The effects of Apo E ε4 allele is observed regardless of ethnic backgrounds (Tang et al, 1996). Apo E ε4 allele is also a risk factor for cardiovascular and/or neurovascular disease and DLB (Roses, 1997; Hebert, 2000; Singleton, 2001). However, the presence of Apo E ε4 allele doesn’t necessarily lead to the development of AD, as it is not found in about half of senile AD (Pedersen et al, 2004). Apo E ε4 allele is considered to interact with a variety of other factors affecting the onset of AD (Kuusisto et al, 1994; Skoog et al, 1998).

Apo E genotyping for the general population is not recommended. However, presymptomatic genetic counseling is recommended in those likely to have a genetic cause for dementia such as familial AD, FTD, cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy or Huntington’s disease (NICE-SCIE, 2007; Patterson et al, 2008).

(2) Modifiable risk factors

1) Alcohol consumption

When consumed moderately, alcohol might reduce the risk of cardiovascular and/or neurovascular disease, and dementia. Excess consumption of it raises the onset of dementia. A J-shape relationship was reported between alcohol intake and the risk of dementia (Saunders et al, 1991; Letenneur, 2004). Red wine is often mythically believed to have greater protective effects than other types of alcoholic beverage for the above mentioned diseases. This statement, however, is totally groundless, and should not be used to encourage alcohol consumption. The maximum daily alcohol allowances are 2 units for women and 3 units for men (NICE-SCIE, 2007).

2) Smoking

Smoking is a risk factor for almost all types of dementia including AD, and a definitive risk factor for cardiovascular and/or cerebrovascular disease (Ott et al, 1998). The hypothesis that smoking reduces the
onset of AD is based on the study that the number of newly diagnosed AD patients is lower in smokers (Brenner et al, 1993). However such effects of smoking were not observed in many other studies (Fratiglioni, 1993), and smoking was rather reported to increase the risk of AD in a large volume of studies (Launer et al, 1999). A recent epidemiological survey in Korea also showed that the risk of dementia was 1.5 times higher in smokers compared with non-smokers (Korean Ministry of Health and Welfare, 2009).

3) Obesity
The rise in body mass index (BMI) in the middle age is a risk factor for dementia, particularly AD (Gustafson et al, 2003; Kivipelto et al, 2005). BMI increase is also associated with type 2 diabetes which is an independent risk factor of cerebrovascular disease and dementia (Ott et al, 1999; Biessels et al, 2006).

4) Hypertension
Hypertension is a major risk factor for cardiovascular and cerebrovascular disease (Chalmer et al, 2003; Sacco et al, 2006; Williams et al, 2002). Hypertension in the middle age is a risk factor for VaD and AD (Skoog et al, 1996), and is associated with increased pathological findings of AD (Petrovitch et al, 2000). According to the meta-analysis by Feigin et al (2005), treatment of hypertension is effective in preventing not only VaD but AD. Further research is needed to clarify the difference in the preventive effects among various antihypertensives with different modes of action (NICE-SCIE, 2007).

5) Hypercholesterolemia
While hypercholesterolemia might act as a risk factor for some types of dementia (Jick et al, 2000), it is not a universal risk factor for all dementias (Rea et al, 2005). Hypercholesterolemia is a risk factor of stroke that could lead to VaD, and might be a risk factor of AD (Scott et al, 2001). Treatment with statins might lower the onset of AD, though definitive evidence is still lacking. Some guidelines such as NICE-SCIE recommend a statin therapy in patients with AD who have risk factors for cardiovascular disease (NICE-SCIE, 2007).

6) Head injury
Head injury serious enough to cause loss of consciousness (LOC) almost doubles the risk of dementia (Guo et al, 2000; Plassman et al, 2000). The claim that history of head injury increases the risk of dementia is based on the report of the association between boxers and dementia (Merz B, 1989). Mayeux et al (1993) analyzed elderly subjects living in New York, USA, in a controlled study, and reported that the risk of dementia increased in the elderly with history of head injury with LOC. The increase in amyloid production in the brain and cerebrospinal fluid (CSF) has been suggested as a mechanism for the head injury-induced dementia (Olsson et al, 2003). If a person with Apo E ε4 allele sustains head injury with LOC, the risk of dementia increases by 10 times (Guo et al, 2000). One interesting observation is that in the all 15 epidemiological studies on dementia and head injury, the relationship was found only in men (Fleminger et al, 2003). In a recent local epidemiological study, the risk of dementia was over two times higher in the elderly with history of head injury with LOC that lasted longer than 10 minutes, compared
with their controls without such history (Korean Ministry of Health and Welfare, 2009).

7) Depression

The association between depression and dementia is very complicated. The prevalence of depression in patients with dementia is approximately 12%, and depression might appear as a prodromal or early symptom of dementia (Jom, 2000). Patients with depression often have cognitive impairment severe enough to be diagnosed with dementia. It is still inconclusive, however, if depression is a prodrome to dementia, if the two conditions have common risk factors, and if depression and/or depression-related inflammation or corticotoxicity increases the risk of dementia. To put together current evidence, depression is a risk factor for dementia, and history of depression might increase the risk of secondary dementia (John, 2000, Green et al, 2003). Therefore, it is necessary to include diagnostic tools for depression when evaluating cognitive functioning of dementia patients. Such tools of wide use include the geriatric depression scale, the center for epidemiologic studies depression scale, and the Hamilton depression scale (Burke et al, 1991; Andresen et al, 1994; Hamilton et al, 1960). A recent epidemiological survey in Korea reported that depression was associated with a three-fold increase in the risk of dementia (Korean Ministry of Health and Welfare, 2009).

8) Thyroid disorder and other metabolic disease related to dementia

Hypothyroidism is common in the elderly (Luboshitzky et al, 1996). In the cognitive testing, the elderly with hypothyroidism who were without dementia symptoms showed poorer performance compared with the normal controls in areas of word fluency, visuospatial abilities, and learning abilities (Osterweil et al, 1992; Lindeman et al, 1999). While no data exists on the association of TSH fluctuation and cognitive function, it has been reported that an elevated TSH might contribute to the increase in the risk of dementia (Ganguli et al, 1996). The proportion of thyroid-linked dementia was shown relatively smaller in recent studies, which might be because thyroid disorder is diagnosed before it gets serious enough to affect cognitive functions (White et al, 1996; Clarfield et al, 1988). Other dementia-related metabolic abnormalities include parathyroid dysfunction, Addison’s disease, hypoglycemia, hepatic encephalopathy, uremia, hypoxia, electrolyte disturbances, and vitamin deficiencies (Weytingh et al, 1995).

9) Syphilis

It is controversial if syphilis testing should be included in the routine dementia screening in patients at a low environmental risk of getting the infection (Petersen, 2001). In general, the VDRL test, rapid plasma reagin, and the fluorescent treponemal antibody test are included in the routine dementia screening in regional areas with a high prevalence of syphilis, in patients at high risk, or in cases where the prevalence or risk is hard to determine (Powell et al, 1993; Siu, 1991).

10) Vitamin B12, folate, and homocysteine

Vitamin B12 deficiency often leads to lower-than-normal cognitive functions. However, definitive evidence is lacking that such cognitive decline increases the risk of dementia (Crystal et al, 1994). Folate deficiency might be a risk factor not only for cardiovascular and/or cerebrovascular disease but for dementia including AD (Seshadri et al, 2002). The level of homocysteine is inversely related to the folate
level and is lowered by folate intake. While intake of vitamin B12 and folate was not shown to reduce the risk of dementia in one study, future results might be noteworthy as extensive research is currently under way (Malouf et al, 2003).

(3) Other risk factors

1) Atrial fibrillation

Further evidence is needed to determine if atrial fibrillation is a risk factor for dementia (Ott et al, 1997).

2) Consumption of saturated fat

Further evidence is needed to determine if consumption of saturated fat is a risk factor for dementia (Mental Health Foundation, 2006).

3) History of a serious psychiatric disease and/or schizophrenia

As an environmental factor, serious psychiatric illness or schizophrenia increases the risk of dementia (NICE-SCIE, 2007).

4) Occupational exposure to heavy metals

There is no evidence that a direct exposure to lead or solvents causes AD. Though aluminum is neurotoxic, no evidence is available to suggest that it causes chronic neuronal degenerations including AD (Doll et al, 1993).

2. Protective factors of dementia

1) Exercise

Exercise has a positive effect on cardiovascular health, bone density, and mood stability. It also improves interpersonal relationship. Physical activities in the middle age reduce the risk of dementia and AD. The recommended exercise regimen is at least twice a week, more than 30 minutes at a time, hard enough to break a sweat or become slightly out of breath. Steady workout as recommended could cut the risk of dementia and AD in half (Rovio et al, 2005).

2) Education and mental stimulation

Research suggests that the risk of dementia is inversely related to the level of education, and that reduced mental activity in childhood depletes brain reserves, facilitating development of dementia symptoms (Stem et al, 1994; Valenzuela et al, 2005). On the other hand, higher levels of education or higher pre-morbid intelligence are believed to have protective effects against the development of dementia symptoms. Aging process was faster in those with decreased intelligence compared with normal, and the prevalence of dementia was 3 to 4 times higher in those with decreased intelligence group without Down syndrome (NICE-SCIE, 2007). In a recent epidemiological survey by Korean Ministry of Health and Welfare, the risk of dementia was 1.6 times and 4.5 times higher in the elderly with the education years of ≤6 and in the elderly with no education, respectively, compared with the elderly with higher levels of education (Korean Ministry of Health and Welfare, 2009)

Continuous brain activity might reduce the onset of dementia and AD (the ‘use it or lose it’ hypothesis). In addition, those with higher intelligence might have a delayed symptom development compared with
those without (the cerebral reserve hypothesis). Indeed, cognitive engagement reduced the risk of AD (Wilson et al, 2002), and participation in cognitive trainings or cognitive leisure activities was proven protective against dementia (Ball et al, 2002; Verghese et al, 2003). Leisure activities that require cognitive functioning include reading, board games (checkers, chess, card games etc), musical instrument playing, and dancing. Such intellectual activities are believed to have brain-protective effects (NICE-SCIE, 2007).

3) Non-steroidal anti-inflammatory drugs

One study based on the inflammatory hypothesis in AD (McGeer et al, 1999) reported that Non-steroidal anti-inflammatory drugs (NSAIDs) could prevent dementia, particularly AD (De Craen et al, 2005). The risk reduction by NSAIDs was approximately 50% in retrospective studies whereas 20% in prospective studies. The discrepancy seems attributable to the recall bias. The preventive effects of NSAIDs was greater in those with the APOE ε4 allele (Yip et al, 2005), and more significant in the long-term users of 2 years or more (Szekely et al, 2004; Etminan et al, 2003). Chronic use of NSAIDs, however, might cause multiple adverse reactions, with the vulnerability increasing with age. Further research is needed into the doses, types, duration, and potential benefits and risks of NSAIDs in the context of dementia prevention.

4) Antioxidants

Oxidative damage is related to the pathological changes in dementia or AD (Retz et al, 1998). A continuous stream of researchers has suggested that antioxidants reduce free radicals and thus protect brain against the effects of aging. Studies have produced contradictory results about the protective effects of vitamin C (ascorbic acid) and vitamin E (D-alpha-tocopherol acetate) for AD (Boothby et al, 2005; Zandi et al, 2004; Luchsinger et al, 2003). In a prospective cohort study that followed up 815 community seniors for a mean period of 4 years from 1993, vitamin E intake significantly reduced the risk of AD (Morris et al, 2002). In another study, however, uninterrupted consumption of high-dose vitamin E for over 1 year raised bleeding tendency and subsequent mortality, and also increased heart failure in patients with diabetes or other preceding vascular diseases (Miller et al, 2005, Lonn et al, 2005). From the study results available, it is not preferable to recommend vitamin E for primary or secondary prevention of AD or dementia (Boothby et al, 2005). No definitive evidence is available regarding the use of high-dose vitamin C in this context (NICE-SCIE, 2007).

5) Hormone replacement therapy

Based on the epidemiological observations that AD was more common in women and that the rate of AD or dementia was lower in women receiving hormone replacement therapy (HRT), studies investigated if HRT delayed or prevented the onset of dementia, particularly AD. The evidence is still weak to support that HRT improves cognitive functioning in normal elderly women (Hogervorst et al, 2002). The preventive effect was not supported either in another analysis of HRT and the risk of dementia (Low et al, 2006). In a recent large-scale prospective study (Women's Health Memory Study), HRT showed little preventive effects against dementia, while the rate of dementia was rather twice in the HRT group (Shumaker et al,
3. Summary of risk / protective factors of dementia

The risk and protective factors for dementia are summarized below in terms of their modifiability and the strength of supporting evidence.

1) Risk factors of dementia
① Non-modifiable risk factors;
Advanced age, genotype, female gender, and learning disability
② Established modifiable risk factors:
Hypertension, stroke, smoking, excessive alcohol consumption, diabetes, depression, and head injury
③ Possible modifiable risk factors:
Obesity, hyperhomocysteinemia, and hypercholesterolemia

2) Protective factors of dementia
① Established protective factors:
Long-term use of NSAIDs, control of vascular risk factors, regular exercise, and engagement in leisure and cognition-stimulating activities
② Possible protective factors:
Antidepressant therapy, statin therapy, and hormone replacement therapy

4. Significance of controlling vascular risk factors and early dementia management

Known vascular risk factors associated with AD include hypertension, diabetes, hypercholesterolemia, smoking, and obesity. Vascular protective factors associated with AD, on the other hand, are exercise and moderate drinking (Morris, 2003). Risk factors for VaD are stroke and its risk factors such as hypertension, heart disease, diabetes, hyperlipidemia, hyperhomocysteinemia, alcohol drinking, and mental stress (Gorelick et al, 1997). Smoking, hypertension, diabetes are independent risk factors for AD and VaD, with hyperlipidemia added for the latter. All risk factors for stroke are risk factors for atherosclerosis-related dementia. Vascular lesions such as stroke contributed to the elevated risk of AD (Ritchie et al, 2002), and were reported as part of the pathological interaction leading to AD symptom presentation (Snowdon et al, 1997; Vermeer et al, 2003). As many of the risk factors for stroke are shared with AD, and as cerebral ischemia has gained significance as a cause of AD, one can conclude that intensive control and treatment of hypertension, diabetes, smoking, obesity, heart disease, and hyperlipidemia is imperative for prevention and treatment of not only VaD but AD.

Both AD and VaD have a number of modifiable vascular risk factors. Recent epidemiological studies suggest that their aggressive control might eventually lead to primary prevention and a reduced onset of dementia. Therefore, early and intensive control of modifiable vascular risk factors is critical in preventing and treating AD and VaD as well as cardiovascular and/or cerebrovascular disease.
Considering the natural cognitive decline associated with aging, a routine dementia screening for the general population should be determined carefully. Evidence is weak to perform a cognitive testing in individuals without symptoms of cognitive decline. The preventive efforts, however, need to begin desirably in the 40s, given that management of the vascular risk factors is important for dementia prevention, that prevention of cardiovascular and cerebrovascular disease requires control of the risk factors beginning from the age of 40s, and that the cerebral pathological changes in AD start 15 to 20 years earlier than symptom presentation.
Recommendations

1. Medical intervention aimed at early detection and prevention of dementia should be implemented as a 5-year delay in the onset of dementia is known to cut the prevalence by half (Level A).

2. Periodic and continuous medical intervention alert to any changes in the cognitive function and the activities of daily living performance should be implemented in patients with suspected mild cognitive impairment (Level B).

3. Early detection of the risk factors of dementia and subsequent medical intervention is important for prevention of dementia. A thorough control of the vascular risk factors is particularly critical for prevention and management of not only cardiovascular and/or cerebrovascular disease but dementia (Level A).
References


Boothby L.A, Doering PL. Vitamin C and Vitamin E for Alzheimer’s disease. The Ann Pharmacother,


Schellenberg GD, Anderson L, O’dahl S, Wisjman EM, Sadovnick AD, Ball MJ, Larson EB, Kukull WA,


Weytingh MD, Bossuyt PM, van Crevel H. Reversible dementia: more than 10% or less than 1%? A quantitative review. J Neurol. 1995;242:466–471.


Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA.


Chapter 2. Diagnosis and Evaluation of Dementia

Clinical diagnosis of dementia is made by the following criteria; 1) acquired multiple cognitive deficits are present, 2) they are serious enough to interfere with the activities of daily living (ADL), and 3) they are not part of the course of delirium. Dementia does not refer to a single illness, but a clinical syndrome that has about 70 different clinical causes. Alzheimer’s disease (AD), a degenerative brain disorder, accounts for 40-80% of total dementia. Though there is no radical treatment to AD, there are many other reversible, preventable and controllable causes or factors of dementia are present whose symptomatic improvement or complete reversal is possible with treatment of underlying diseases. Therefore accurate diagnosis and/or differentiation of a dementia subtype are imperative. Differential diagnosis has gained an increasing significance in the treatment context as well, since, for example, the side effects of antipsychotics are particularly vulnerable in patients with Dementia with Lewy Bodies (DLB). This chapter describes the process for diagnosis and assessment of dementia.

A. General diagnostic workup of dementia

Before patient evaluation, it is necessary to identify if the patient or members of the family want to be informed of the diagnosis, and to whom the patient information should be disclosed. Then comprehensive assessments for the diagnosis of dementia as shown below;

1. History taking and assessment of cognition
2. Physical and neurological examinations
3. Standardized neuropsychological tests
4. Assessment of the ADL performance
5. Laboratory tests
6. Brain imaging

Once dementia is diagnosed based on the results, a specific cause is identified using the diagnostic criteria for each dementia subtype. While diagnosis of dementia can be made in the primary healthcare setting, a specific subtype is ideally and generally diagnosed by dementia specialists after referral. Other necessary evaluations include medical comorbidity, drugs in use, and behavioral and psychological symptoms of dementia (BPSD) such as depressive or psychiatric symptoms. The general diagnostic work-up of dementia is presented below.
B. Evaluation of dementia
1. History taking and assessment of cognition

A thorough history taking is a cornerstone of assessing patients suspected of dementia. The history should include the mode of onset, the pattern of progression, cognitive manifestations, and behavioral changes. The information should be sufficient enough for application of the diagnosis criteria. Past medical history, current co-morbidities, family history and education history are important. Assessment of ADL and BPSD including depression, delusion, and hallucination provides information necessary not only for diagnosis but patient management later.

Due both to the presence of cognitive deficit and to the possibility of anosognosia, it is important to obtain a history from a reliable informant such as a family member or relative. Patients with subjective memory impairment might complain of depression or anxiety symptoms, but the complaints should be reviewed carefully to differentiate prodromal symptoms of dementia (Jonker et al, 2000).

For efficient history taking from patients or care-givers, it is useful to take history for each cognitive domain. Regarding memory, patients are questioned if they are forgetful of appointments, ask the same questions repeatedly, or frequently fail to remember where they’ve left items and search for them. Questions for the language domain include if the patients find it hard to come up with the suitable words or expressions. For the visuospatial domain, patients are questioned if they get often disoriented and end up getting lost. Reduced calculation skills such as payment errors at a cashier or difficulty in handling financial matters should also be questioned. If the frontal lobe is affected, judgment or impulse control is impaired, giving the impression of personality change or emotional fluctuations. For example, a formerly meticulous person might become laid-back, or a talkative and social person might turn quiet and apathy, preferring to stay at home. Other check points include if the thought process has been simplified or if he
or she has turned selfish or doubtful of others. One consideration here is that while cognitive decline, even to a slight degree, is easily detected at an early stage in those with active social engagement, the chance is low in those who mostly stay at home. Assessment of ADL needs to be based on comparison with the previous level of performance.

Standardized and localized tools for informant assessment are useful to gather information about patients. They include the Korean Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-K) (Lee et al, 2005), the Short Samsung Dementia Questionnaire (S-SDQ) (Choi et al, 1999), and the Seoul Informant Report Questionnaire for Dementia (SIRQD) (Lee et al, 2004).

BPSD refers to signs and symptoms of disturbed perception, thought contents, mood, or behavior in patients with dementia (Finkel 1997). It is common, found in about 90% of dementia patients (Lyketsos et al, 2002). BPSD accelerates the decline in cognitive function and ADL performance, leading to early admission into nursing facilities or healthcare institutions, increased mortalities, and augmented psychological and financial burdens for care givers (Knopman et al, 1999, Levy et al, 1996, Lopez et al, 1999). The standardized BPSD assessment tools used in the clinical practice of Korea include the Korean Neuropsychiatric Inventory (K-NPI) (Choi et al, 2000) and the Korean Behavior Rating Scale for Dementia (BRSD-K) (Yoon et al, 2008).

2. Physical and neurological examinations

Routine physical and neurological examinations are performed to detect somatic and neurological signs of abnormalities. The neurological tests in early AD are unremarkable apart from the cognitive impairment. However, for many other dementing disorders, for example DLB and prion diseases, the presence of additional neurological features such as an extrapyramidal syndrome or myoclonus is a key component of the diagnostic criteria. Therefore, a physical and neurological examination makes an important part of the diagnosis of dementia.

3. Standardized neuropsychological tests

Cognitive assessment is important for several reasons. First, the diagnosis of dementia mainly relies on the evidence of multiple cognitive deficits (their presence and/or absence and severity). Second, most of causes of dementia can be identified by the nature of their cognitive and behavioral changes. Third follow-up neuropsychological tests help identify the disease progression. As an increasing number of patients in the early stage of dementia, it is now important to assess cognitive function at a prodromal phase. Accordingly, an evaluation of cognitive function is required for the diagnosis and treatment in a prodromal, mild, or moderate stage of dementia, whereas it is less essential for severely demented patients. Cognitive assessment consists of brief cognitive tests and more comprehensive neuropsychological batteries.

1) Brief cognitive tests
They are used mainly for early evaluation of cognitive impairment, as in the first stage screening of dementia or mental state assessment during history taking. Instruments for dementia screening need to have 1) a short test time, 2) an easy application and scoring, 3) a high sensitivity and specificity, and 4) insusceptibility to influence by education, gender, and age. The most widely used standardized tool for brief cognitive assessment is the Mini Mental State Examination (MMSE) (Folstein et al, 1975). Other useful tests include the Revised Hasegawa’s Dementia Scale (HDS-R) (Imai and Hasegawa 1994), the 7 Minute Screen (7-MS) (Meulen et al, 2004), the clock drawing test, the Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005). In Korea, several standardized versions of MMSE are available, including MMSE-K (Kwon et al, 1989), K-MMSE (Kang et al, 1997), MMSE-KC (Lee et al, 2002) and MMSE-DS (Han et al). HDS has two standardized Korean version; HDS-K (Kim et al, 2002) and K-HDS (Yang et al, 2004). Other Korean versions of brief cognitive assessment scales include the Short Blessed Test of Korea (SBT-K) (Lee et al, 1999), the 7-MS of Korea (7-MSK) (Park et al, 2002), the MoCA of Korea (MoCA-K) (Lee et al, 2008), and Korean-MoCA(7-KMoCA) (Kang et al, 2009). Limitations to these brief assessment tools include 1) insensitivity to the upper and lower limits of the cognitive continuum, as well as to some subtypes of dementia such as frontotemporal dementia (FTD) or vascular dementia (VaD). and 2) neglect of some cognitive domains such as executive functions. Therefore, when interpreting the test scores, one should fully take into consideration the effects of compound variables such as age, education, gender, occupation, language, prior cognitive level, visual or auditory ststus, physical and psychiatric conditions.

2) Neuropsychological batteries
A comprehensive neuropsychological battery is used to differentiate a questionable or mild dementia from normal cognitive decline, to differentiate among subtypes of dementia, and to provide the baseline cognitive data necessary for measurement of treatment response. A neuropsychological battery assesses variable cognitive domains including memory, language, attention, judgment, calculation, executive functioning, and visuospatial abilities. The standardized neuropsychological batteries used in Korea include the Korean version of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD-K) (Lee et al, 2004, Lee et al, 2002), the Korean version of the Alzheimer’s Disease Assessment Scale (ADAS-K) (Yoon et al, 2002), and the Seoul Neuropsychological Screening Battery (SNSB) (Kang et al, 2003). Useful in severe dementia, two Korean versions of the Severe Impairment Battery (SIB) have been developed and used (Ahn et al, 2006, Nah et al, 2006).

4. Assessment of activities of daily living
Depending on definitions of dementia, decline in every day functional abilities is a major component of the diagnosis of dementia. It has a great influence on the quantity and quality of care. Assessment of function in daily life is part of the diagnostic process, and allows clinicians to evaluate the degree of patient independence and the need for care, aiding in planning of dementia care. ADL is also tested as part of the clinical assessment of the effects of treatment interventions including medications and the ADL
skill trainings. Different scales are used to objectively measure these abilities, most of which are based on the interview with the patient and his/her care-giver. The two classical fields that are measured are basic physical activities (such as eating, dressing, personal hygiene, etc.) and instrumental activities (such as use of devices and shopping). Standardized ADL assessment tools currently in use in Korea include the Korean version of the Instrumental Activity of Daily Living (K-IADL) (Kang et al, 2002), the Korean version of the Activity of Daily Living (K-ADL) (Won et al, 2002), the Korean version of the Disability Assessment for Dementia (K-DAD) (Seo, 2003), the Korean version of the Bayer Activity of Daily Living (B-ADL) (Choi et al, 2003), the Seoul- Instrumental Activities of Daily Living (S-IADL) (Ku et al, 2004), and the Seoul- Activities of Daily living (S-ADL) (Ku et al, 2004b).

5. Laboratory tests
Though there is no broad consensus over the laboratory test items to be included in the evaluation of patients suspected dementia, most of the clinical practice guidelines for dementia offer similar recommendations (Beck et al, 2000). The objectives of the laboratory tests are to identify comorbidity common in the elderly and to rule out any medical conditions that might affect cognitive impairment or act as a reversible cause of dementia. Routine laboratory tests for dementia include complete blood count, biochemical profile (electrolytes, blood glucose, calcium, renal and/or hepatic functions etc.), thyroid function, and serum vitamin B12 and folate levels. Serum syphilis and human immunodeficiency virus tests are recommended in those presenting with medical history or clinical symptoms that cause suspicion. Other tests including chest X-ray, electrocardiogram, urinalysis, and lipid analysis are done if necessary. A routine cerebrospinal fluid or genetic test are not recommended for the diagnostic purpose alone.

6. Brain imaging
1) Structural brain imaging
Structural brain imaging includes Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). The latter, while more costly, is superior to CT in visualizing the structural lesions and anatomical abnormalities such as white matter changes. The objectives of using structural brain imaging in the diagnosis of dementia are to exclude cerebral hemispheric lesions that could cause cognitive deficits (space-occupying lesions, subdural lesions, normal pressure hydrocephalus, etc) and to obtain brain scans needed for differential diagnosis of dementia subtypes (for example, differentiating AD from VaD or FTD). A routine use of CT or MRI is recommended for early evaluation of dementia.

2) Functional brain imaging
Functional brain imaging includes Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). HeMaethylPropyleneAmine Oxime (HMPAO) SPECT and 18F-fluoro-2-deoxy-D-glucose (FDG) PET are commonly used for the diagnosis and assessment of dementia.
Measuring the cerebral blood flow and brain glucose metabolism using radioactive isotopes to identify dysfunctions in different brain regions, both PET and SPECT are useful for differentiation among AD, VaD, or FTD. They can also detect a brain function decline in early AD that present no abnormal findings in the structural brain imaging, and are therefore useful for early diagnosis. In particular, SPECT is known superior to FDG PET in the diagnosis of AD, showing a higher sensitivity and specificity (Mielke and Heiss 1998).

C. Diagnostic criteria for dementia by subtype
1. Diagnostic criteria for Alzheimer’s disease

A wide variety of diagnostic criteria for AD have been developed so far. The most commonly used home and abroad are Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association (McKhann et al, 1984) (Table 2). Also of wide use in Korea is the Korean Classification of Disease, a variation from the ICD-10 (Table 3), mostly used to insurance claim process and to determine a cause of death (Cooper 1989). Both the DSM-IV criteria for ‘dementia of the Alzheimer’s type’ and the NINCDS-ADRDA criteria for ‘probable Alzheimer’s disease’ have shown preferable diagnostic sensitivity (a mean of 81%) and specificity (a mean of 70%), but the NINCDS-ADRDA criteria for ‘possible Alzheimer’s disease’ showed a lower specificity (a mean of 48%) and a higher sensitivity (a mean of 83%) compared with the criteria for ‘probable Alzheimer’s disease’ (Knopman et al, 2001).

Table 1. DSM-IV Diagnostic Criteria for Dementia of the Alzheimer’s Type

<table>
<thead>
<tr>
<th>A.</th>
<th>The development of multiple cognitive deficits manifested by both</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>memory impairment (impaired ability to learn new information or to recall previously learned information)</td>
</tr>
<tr>
<td>2.</td>
<td>one (or more) of the following cognitive disturbances:</td>
</tr>
<tr>
<td>(a)</td>
<td>aphasia (language disturbance)</td>
</tr>
<tr>
<td>(b)</td>
<td>apraxia (impaired ability to carry out motor activities despite intact motor function)</td>
</tr>
<tr>
<td>(c)</td>
<td>agnosia (failure to recognize or identify objects despite intact sensory function)</td>
</tr>
<tr>
<td>(d)</td>
<td>disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)</td>
</tr>
</tbody>
</table>

| B. | The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning. |

| C. | The course is characterized by gradual onset and continuing cognitive decline. |

| D. | The cognitive deficits in Criteria A1 and A2 are not due to any of the following: |

| 1. | other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson’s disease, Huntington’s disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor) |
| 2. | systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection) |
| 3. | substance-induced conditions |

| E. | The deficits do not occur exclusively during the course of a delirium. |
The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Table 2. NINCDS-ADRDA Criteria for Diagnosis of Alzheimer Disease

<table>
<thead>
<tr>
<th>I.</th>
<th>Clinical Diagnosis of Probable Alzheimer's Disease</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dementia established by clinical examination and mental status testing and confirmed by neuropsychological testing</td>
</tr>
<tr>
<td>2.</td>
<td>Deficits in at least two cognitive domains</td>
</tr>
<tr>
<td>3.</td>
<td>Progressive cognitive decline, including memory</td>
</tr>
<tr>
<td>4.</td>
<td>Normal level of consciousness</td>
</tr>
<tr>
<td>5.</td>
<td>Onset between ages 40 and 90 (most common after 65) years</td>
</tr>
<tr>
<td>6.</td>
<td>No other possible medical or neurological explanation</td>
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<tr>
<th>II.</th>
<th>Probable Alzheimer's Disease Diagnosis Supported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Progressive aphasia, apraxia, and agnosia</td>
</tr>
<tr>
<td>2.</td>
<td>Impaired activities of daily living</td>
</tr>
<tr>
<td>3.</td>
<td>Family history of similar disorder</td>
</tr>
<tr>
<td>4.</td>
<td>Brain atrophy on CT/MRI, especially if progressive</td>
</tr>
<tr>
<td>5.</td>
<td>Normal CSF, EEG (or nonspecifically abnormal)</td>
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</table>

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<tr>
<th>III.</th>
<th>Other Clinical Features Consistent with Probable Alzheimer's Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Plateau in course</td>
</tr>
<tr>
<td>2.</td>
<td>Associated symptoms: depression; insomnia; incontinence; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; weight loss; during more advanced stages increased muscle tone, myoclonus, and abnormal gait</td>
</tr>
<tr>
<td>3.</td>
<td>Seizures in advanced disease</td>
</tr>
<tr>
<td>4.</td>
<td>CT normal for age</td>
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<tr>
<th>IV.</th>
<th>Features That Make Alzheimer's Disease Uncertain or Unlikely</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Acute onset</td>
</tr>
<tr>
<td>2.</td>
<td>Focal sensorimotor signs</td>
</tr>
<tr>
<td>3.</td>
<td>Seizures or gait disorder early in course</td>
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<tr>
<th>V.</th>
<th>Clinical Diagnosis of Possible Alzheimer's Disease</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Dementia with atypical onset or course in the absence of another medical/neuropsychiatric explanation</td>
</tr>
<tr>
<td>2.</td>
<td>Dementia with another disease not felt otherwise to be the cause of dementia</td>
</tr>
<tr>
<td>3.</td>
<td>For research purposes, a progressive focal cognitive deficit</td>
</tr>
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<th>VI.</th>
<th>Definite Alzheimer's Disease</th>
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<tbody>
<tr>
<td>4.</td>
<td>Meets clinical criteria for probable Alzheimer's disease</td>
</tr>
<tr>
<td>5.</td>
<td>Tissue confirmation (autopsy or brain biopsy)</td>
</tr>
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<th>VII.</th>
<th>Research Classification of Alzheimer's disease should specify</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Familial?</td>
</tr>
<tr>
<td>2.</td>
<td>Early onset (before age 65)?</td>
</tr>
<tr>
<td>3.</td>
<td>Down's syndrome (trisomy 21)?</td>
</tr>
<tr>
<td>4.</td>
<td>Coexistent other neurodegenerative disease (e.g., Parkinson's disease)?</td>
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### Table 3. ICD-10 Criteria for Diagnosis of Alzheimer Disease

#### A. The general criteria for dementia (G1 to G4) must be met.

**G1.** Evidence of each of the following:

1. A decline in memory, which is most evident in the learning of new information, although in more severe cases, the recall of previously learned information may be also affected. The impairment applies to both verbal and non-verbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.

   The severity of the decline, with mild impairment as the threshold for diagnosis, should be assessed as follows:

   **Mild:** A degree of memory loss sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living (see comment on cultural aspects of "independent living" on page 24). The main function affected is the learning of new material. For example, the individual has difficulty in registering, storing and recalling elements in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.

   **Moderate:** A degree of memory loss which represents a serious handicap to independent living. Only highly learned or very familiar material is retained. New information is retained only occasionally and very briefly. The individual is unable to recall basic information about where he lives, what he has recently been doing, or the names of familiar persons.

   **Severe:** A degree of memory loss characterized by the complete inability to retain new information. Only fragments of previously learned information remain. The subject fails to recognize even close relatives.

2. A decline in emotional control or motivation, or a change in social behaviour, manifest as at least one of the following:

   **(1)** emotional lability;

   **(2)** irritability;

   **(3)** apathy;

   **(4)** coarsening of social behaviour.

3. For a confident clinical diagnosis, G1 should have been present for at least six months; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

   **Comments:** The diagnosis is further supported by evidence of damage to other higher cortical functions, such as aphasia, agnosia, apraxia.

   Judgment about independent living or the development of dependence (upon others) need to take account of the cultural expectation and context.

   Dementia is specified here as having a minimum duration of six months to avoid confusion with reversible states with identical behavioural syndromes, such as traumatic subdural haemorrhage, normal pressure hydrocephalus and diffuse or focal brain injury.

#### B. There is no evidence from the history, physical examination or special investigations for any other possible cause of dementia (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), a systemic disorder (e.g. hypothyroidism, vit. B12 or folic acid deficiency, hypercalcaemia), or alcohol- or drug-abuse.

---

### 2. Diagnostic criteria for vascular dementia

Currently available diagnostic criteria for VaD include DSM-IV (Table 4), the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en
Neurosciences (NINDS-AIREN) (Roman et al, 1993) (Table 5), International Classification of Disease-10 (ICD-10) (Table 6), and the Modified Hachinski Ischaemic Score (HIS) (Hachinski et al, 1975; Rosen et al, 1980) (Table 7). Different sets of the diagnostic criteria for VaD could not be interchanged and showed poor diagnostic sensitivity. They particularly fail to reflect the effects of white matter lesions (Pohjasvaara et al, 2000). The NINDS-AIREN criteria are commonly used in the clinical practice and research field for the diagnostic purpose. The requested clear temporal relationship between dementia and cerebrovascular events made the lower sensitivity of the NINDS-AIREN criteria in the following conditions: The gradual progression of dementia, absence of the temporal relationship with cerebrovascular events, or coexisting pathology of AD (Chui et al, 2000, Ransmayr 1998). The NINDS-AIREN criteria for ‘probable vascular dementia’ show a sensitivity of 13% and a specificity of 98%. The rates are 70% and 76% with the DSM-IV criteria for VaD, and 70% and 80% respectively with the ICD-10 criteria for VaD (Knopman et al, 2003).

Table 4. DSM-IV criteria for the diagnosis of vascular dementia

| A. | The development of multiple cognitive deficits manifested by both: Memory impairment (impaired ability to learn new information or to recall previously learned information) One or more of the following cognitive disturbances: (a) Aphasia (language disturbance) (b) Apraxia (impaired ability to carry out motor activities despite intact motor function) (c) Agnosia (failure to recognize or identify objects despite intact sensory function) (d) Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting) |
| B. | The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning. |
| C. | Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance. |
| D. | The deficits do not occur exclusively during the course of a delirium |

Table 5. NINDS-AIREN criteria for the diagnosis of vascular dementia

| I. | The criteria for the clinical diagnosis of probable vascular dementia include all of the following: 1. *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone. *Exclusion criteria*: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition. 2. Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of not relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof. 3. A *relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits. |
| II. | Clinical features consistent with the diagnosis of probable vascular dementia include the following: |
(a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include (a) early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging; (b) absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of possible vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of definite vascular dementia are (a) clinical criteria for probable vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term "AD with CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

### Table 6. ICD-10 Criteria for Diagnosis of Vascular Dementia

<table>
<thead>
<tr>
<th>A. The general criteria for dementia (G1 to G4) must be met. (See Table 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Unequal distribution of deficits in higher cognitive functions, with some affected and others relatively spared. Thus memory may be quite markedly affected while thinking, reasoning and information processing may show only mild decline.</td>
</tr>
<tr>
<td>C. There is clinical evidence of focal brain damage, manifest as at least one of the following:</td>
</tr>
<tr>
<td>(1) unilateral spastic weakness of the limbs;</td>
</tr>
<tr>
<td>(2) unilaterally increased tendon reflexes;</td>
</tr>
<tr>
<td>(3) an extensor plantar response;</td>
</tr>
<tr>
<td>(4) pseudobulbar palsy.</td>
</tr>
<tr>
<td>D. There is evidence from the history, examination, or tests, of a significant cerebrovascular disease, which may reasonably be judged to be etiologically related to the dementia (e.g. a history of stroke; evidence of cerebral infarction).</td>
</tr>
</tbody>
</table>

The following criteria may be used to differentiate subtypes of vascular dementia, but it should be remembered that the usefulness of this subdivision may not be generally accepted.

### Table 7. Modified Hachinski ischemic scale

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Somatic complaint</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>History of stroke</td>
<td>2</td>
</tr>
</tbody>
</table>
3. Diagnostic criteria for mild cognitive impairment

It has been known in the early 1980s that cognitive deficits without dementia in fact constituted a prodrome of dementia. The condition has since been classified as mild cognitive impairment (MCI). Several other terms are used without distinction (Table 8).

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Senescent Forgetfulness (BSF)</td>
<td>Coined by Kral VA, the term refers to mild memory decline associated with normal aging. Suggested by the National Institute of Mental Health, the term implies a normal aging process. Subjects aged 50 and older with gradual memory loss are classified as having AAMI if they score 1 SD below the mean of younger adults (aged 20~35) in a standardized memory test. Their cognitive functions are in the normal range of the same age peers. Daily living is not impaired.</td>
</tr>
<tr>
<td>Age-Related Cognitive Decline (ARCD)</td>
<td>Proposed by the International Psychogeriatric Association, the concept was reflected in the DSM-IV. Subjects have impairment in at least 1 of the cognitive domains of learning, memory, attention, thinking, language, and visuospatial skills that is ≥1 SD below the education- and age-adjusted normal controls and lasting for at least 6 months.</td>
</tr>
<tr>
<td>Cognitive Impairment Not Dementia (CIND)</td>
<td>Used in the Canadian Study of Health and Aging, the term describes a clinical group of subjects who have impaired memory or other cognitive functions but not meeting the DSM-IV criteria for dementia. The risk of progressing to dementia is high in this group.</td>
</tr>
<tr>
<td>Mild Cognitive Impairment (MCI)</td>
<td>Suggested by Petersen RC, the term refers to a subgroup of the CIND group with marked memory impairment highly likely to indicate a pre-clinical phase of AD.</td>
</tr>
<tr>
<td>Vascular Cognitive Impairment (VCI)</td>
<td>Collectively describing cognitive declines associated with cerebrovascular disease, the term describes a broad clinical group including those with VaD.</td>
</tr>
</tbody>
</table>

Of them, the most commonly used is the one suggested by Petersen, though it only covers amnestic MCI (Table 9). Winblad et al further classified MCI by presence/absence of memory impairment (amnestic or non-amnestic) and the number of domains affected (single or multi domain) (Winblad et al, 2004) (Figure 2.) (Table 10). Single domain amnestic MCI should be monitored for progression into AD, whereas
single domain non-amnestic MCI should be monitored for progression into FTD or DLB. Multi-domain MCI is highly likely to have progressed from single domain MCI, and has the potential to progress to any types of dementia (Petersen et al, 2001).

Table 9. Amnestic Mild Cognitive Impairment Criteria proposed by Petersen RJ

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory complaint preferably corroborated by an informant</td>
</tr>
<tr>
<td>Objective memory impairment for age</td>
</tr>
<tr>
<td>Largely preserved general cognition</td>
</tr>
<tr>
<td>Essentially normal activities of daily living</td>
</tr>
<tr>
<td>Not demented</td>
</tr>
</tbody>
</table>

**Figure 2. The subtype of Mild Cognitive Impairment**

Table 10. Recommendations for the General Criteria for Mild Cognitive Impairment proposed by the International Working Group

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome)</td>
</tr>
<tr>
<td>Cognitive decline</td>
</tr>
<tr>
<td>1. Self and/or informant report and impairment on objective cognitive tasks and / or</td>
</tr>
<tr>
<td>2. Evidence of decline over time on objective cognitive tasks</td>
</tr>
<tr>
<td>3. Preserved basic activities of daily living / minimal</td>
</tr>
<tr>
<td>4. Impairment in complex instrumental functions</td>
</tr>
</tbody>
</table>

Vascular cognitive impairment (Hachinski 1994) is a collective term for cognitive deficits
associated with cerebrovascular disease, regardless of severity of the deficits. Its coverage is broad, from MCI to VaD. As early detection of the cognitive deficits of vascular origin has become increasingly significant, and as the need for the preventive and therapeutic measures have grown, cognitive deficits of cerebrovascular origin that are not dementia have been separately classified as vascular MCI. In this context, the Canadian Study on Health and Aging working group suggested the diagnosis criteria for vascular cognitive impairment with no dementia (CIND) (Ingles et al, 2002, Rockwood et al, 2000) (Table 11). Follow-up of the elderly aged 65+ who had been diagnosed with vascular CIND using the criteria showed that 5 years later, 44% of them progressed into dementia, a rate comparable to the progression rate of amnestic MCI to AD (Canadian Study of Health and Aging Working Group, 2000).

Table 11. The Diagnostic criteria of the vascular cognitive impairment with no dementia proposed by the Canadian Study of Health and Aging Working Group

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The degree of cognitive impairment fails to meet DSM III-R criteria for dementia, which require impairment of memory plus one or more cognitive domains, causing functional deficits.</td>
</tr>
<tr>
<td>2.</td>
<td>The vascular cause of the cognitive impairment is based on presence of signs of ischemia or infarction; e.g., sudden onset, stepwise progression, focal neurological signs, patchy cortical deficits on cognitive testing, evidence of atherosclerosis, and a high Hachinski Ischemic Score.</td>
</tr>
<tr>
<td></td>
<td>The presence vascular risk factors alone is insufficient for a diagnosis of vascular cognitive impairment with no dementia.</td>
</tr>
<tr>
<td>3.</td>
<td>The Global functional impairment is defined as having difficulty any two of the following domains: performing household chore, managing money, feeding self, dressing and incontinence.</td>
</tr>
</tbody>
</table>
Recommendations

1. Diagnosis of dementia should be made through a comprehensive assessment that includes but is not limited to the followings (Level A).
   A. History taking, physical and neurological examinations
   B. Evaluation of cognitive function and mental state using a standardized neuropsychological examination
   C. Assessment of the Activities of Daily Living (ADL)
   D. Brain imaging
   E. Laboratory tests

2. History taking in patients with dementia should obtain sufficient information that includes the followings (Level A).
   A. The mode of onset, the pattern of progression, cognitive impairment, and behavioral changes
   B. Behavioral and psychological symptoms of dementia from a mental state examination
   C. Interviews of reliable informants

3. Cognitive assessment should involve a brief cognitive test and a more detailed neuropsychological battery (Level B).
   A. A brief cognitive assessment is aimed at the early evaluation of patients in the screening of dementia and/or history taking.
   B. A more detailed psychological battery is aimed at differentiating a questionable or mild dementia from normal cognitive decline, differentiating among subtypes of dementia, and providing information for treatment of dementia.
   C. Cognitive assessment should be performed with standardized tools and include memory, language, attention and concentration, judgment, calculation, executive functioning, and visuospatial abilities.

4. ADL impairment is an essential part of the diagnostic criteria for dementia and should be included in the diagnostic evaluation (Level A).
   A. Assessment tools based on the patient and/or carer interviews should be used for an objective ADL assessment.
   B. Both physical and instrumental ADLs should be measured.

5. Laboratory tests of dementia should be aimed at assessing medical states that could affect cognitive functioning or become the primary cause of dementia (Level A).
   A. Laboratory tests of dementia should include CBC, biochemical profile (electrolytes, blood glucose, calcium, renal function, and hepatic function), thyroid function, serum vitamin B₁₂ and folate levels.
   B. A routine cerebrospinal test or genetic test aimed at the diagnosis of dementia is not recommended.
6. Structural and functional brain imaging should be performed for the diagnosis of dementia (Level A).
   A. As a structural brain imaging, CT or MRI should be routinely used in the early evaluation.
   B. As a functional brain imaging, PET or SPECT can be used together with the structural imaging.
References


Meulen EF, Schmand B, van Campen JP, de Koning SJ, Ponds RW, Scheltens P, Verhey FR. The seven minute screen: a neurocognitive screening test highly sensitive to various types of dementia. J
Neurol Neurosurg Psychiatry 2004;75:700-705.


Chapter 3. Cognitive Assessment of Dementia

A clinically applicable, standardized cognitive test is not only important for the objective assessment of the severity of cognitive impairment but is also useful in measuring medical changes over the course of treatment. Questionnaire-type cognitive screening tests taken by caregivers and brief cognitive tests taken by patients are widely used to screen those at risk of dementia before performing a more comprehensive cognitive test. In Korea, a variety of tools for cognitive screening tests and brief cognitive assessment have been standardized using different criteria and are now in clinical use.

Brief cognitive assessment tools mentioned in many of the foreign clinical practice guidelines for dementia include MMSE, 7-MS (the Newcastle Mental Test Score), a clock drawing test (CDT) useful to measure executive functioning, the General Practitioner Assessment of Cognition (GPCOG), and the 6-Item Cognitive Impairment Test (6-CIT) (NICE-SCIE, 2007). This chapter explains the well-known cognitive assessment tools that have been standardized and used in Korea.

A. Cognitive screening tests

Questionnaires for care-givers who live with the patients suspected of dementia have been developed to aid in the diagnosis of dementia. The advantages of the questionnaires as follow: not affected by the patient’s age or education level, applicability to an illiterate patient, sensitive to early stage of dementia and do not need rate training.

1. The Samsung Dementia Questionnaire and the short form Samsung Dementia Questionnaire

The Samsung Dementia Questionnaire (SDQ) is a dementia screening questionnaire based on the changes of cognitive symptoms of the patients suspected of dementia. SDQ should be described by a care-giver who knows the patient well (Choi et al, 1998). It has a total of 32 questions, with a score of 17 or greater establishing the diagnosis of dementia. There was a high correlation between SDQ and MMSE. While not affected by the age or education level of the patient, SDQ is relatively lengthy, its contents focusing mainly memory function and overlapping of some questions. SDQ is not useful for illiterates since some items require reading and writing skills. short form Samsung Dementia Questionnaire (S-SDQ) was developed to improve over the limitations of SDQ. With only 15 questions, shortened from the 32 of SDQ, S-SDQ is quicker to administer. Compared with the dichotomous yes/no scale of SDQ failing to tell the severity of symptoms, S-SDQ employs a 3-point scale, allowing screening of patients with relatively minor symptoms. Absence of reading and writing requirements in S-SDQ, It is applicable to illiterates. While the SDQ cutoff score was 17 (with a sensitivity of 89% and a specificity of 94%), an S-SDQ score of 8 or greater establishes the diagnosis of dementia, regardless of age and education of a patient. The sensitivity (94%) and specificity (90%) didn’t differ much from SDQ (Choi et al, 1999).

2. Korean Dementia Screening Questionnaire

Korean Dementia Screening Questionnaire (KDSQ) is made up of 3 parts, classifying common early
symptoms of dementia into memory impairment, behavioral disturbance (including language disturbance), and activities of daily living (ADL) impairment. Each part contains 5 questions. Absence of writing and reading requirements, it is useful for illiterates. A KDSQ score of 6 or greater (the highest is 15) establishes the diagnosis of dementia (with a sensitivity of 79% and a specificity of 80%). For ADL assessment, five I-ADL questions are included. Notably, questions addressing VaD and depression are interspersed throughout the questionnaire. The 5 questions (KDSQ-H) from the Hachinski Ischemic Scale are aimed at differentiating VaD, providing a clue to the association between the cognitive impairment and vascular causes. A KDSQ-H score of 3 or greater is deemed to suggest a high vascular association. The 5 questions on depression (KDSQ-D) based on the depressive symptoms known to have the biggest impact on the quality of life. KDSQ is known to be highly correlated to the Korean version of the Geriatric Depression Scale (KGDS), but no cutoff point for depression was suggested (Yang et al, 2002).

3. The Korean version of AD8

Previous dementia screening tests have shown limits in community-based research for achieving a prompt and accurate diagnosis of dementia. MMSE is not suitable for for differentiation of early stage of dementia. Influenced by education level, the ceiling and/or floor effects of score are frequently observed in those with a very high and/or low education level. Though education level adjustment is possible, its use is limited in a country like Korea having large uneducated population. The Short Blessed Test (SBT) and the Memory Impairment Screen are simple diagnostic tests of a wide use in other countries, but they are overly weighted toward memory and thus inaccurate in the diagnosis of dementia in which memory impairment is not predominant. A clock drawing test or cube-copying assesses only one cognitive domain. Recently developed to fill the gap and improve detection of early dementia in the highly educated subjects, AD8 is an 8-item questionnaire querying memory (3 items), orientation (1 item), judgment (3 items), and social functions (2 items). When a cut-off of 2 items was used, sensitivity was 74%, and specificity was 85% (Galvin et al, 2005). With simple items and no need for a rater training, AD8 is reported useful for community-based research. It has been standardized in Korea, but not of a clinical use yet (Ryu et al, 2009).

B. Brief cognitive tests

Brief cognitive assessment is used for primary screening in those suspected of cognitive impairment. They are easily and quickly administered after a simple training.

1. Mini-Mental State Examination

A number of established clinical practice guidelines from other countries recommend Mini-Mental State Examination (MMSE) as a screening tool for dementia. Developed by Folstein et al in 1975, MMSE is relatively easy and quick to administer, usually completed in 5 to 10 minutes. It has a low practice effect, and thus can be repeated over the course of disease, allowing a glimpse into the changes over time. With proven reliability and validity in screening of moderate to severe dementia (Kasznia et al, 1986), MMSE is now the most commonly used tool in Korea. Domestic standardized versions include MMSE-K (Kwon et
al, 1989), K-MMSE (Kang et al, 1997), MMSE-KC (Lee et al, 2002) which is also part of CERAD, and
MMSE-DS(Han et al, 2010). The MMSE-K has a total score of 30 (orientation 10, memory registration 3,
memory recall 3, attention and calculation 5, language 7, and reasoning and judgment 2), and
uneducation is adjusted for extra-points. The K-MMSE scoring allocates 5 points to time orientation, 5 to
place orientation, 3 to memory registration, 3 to memory recall, 5 to attention and calculation, 8 to
language, and 1 to visual construction. The total score of K-MMSE is also 30. The MMSE-DS scoring
allocates time orientation, place orientation, memory, attention, language, praxis, visual construction and
abstract thinking. Unlike to MMSE-K, K-MMSE, MMSE-KC and MMSE-DS provide age and years of
education-adjusted norms. While MMSE can be easily administered afar a simple training, it is highly
influenced by the education, age, language difference and cultural background. Other limitations of
MMSE include 1) the lack of items to assess the frontal lobe function, which impedes an accurate
differentiation of frontotemporal dementia (FTD) or vascular dementia (VaD) and 2) the narrow scope of
test make it difficult to to detect or differentiate very mild or profound cognitive impairment.

Table 1. MMSEs standardized in Korea

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Time orientation (5 points)</td>
<td>Time orientation (5 points)</td>
<td>Time orientation (5 points)</td>
<td>Time orientation (5 points)</td>
</tr>
<tr>
<td>10 points</td>
<td>Spatial orientation (5 points);</td>
<td>Spatial orientation (5 points);</td>
<td>Spatial orientation (5 points);</td>
<td>Spatial orientation (5 points);</td>
</tr>
<tr>
<td></td>
<td>The home address and the present location are questioned together</td>
<td>'What kind of a place is this'</td>
<td>'Same as MMSE-K'</td>
<td>'Same as MMSE-K'</td>
</tr>
<tr>
<td></td>
<td>Tree, car, hat</td>
<td>The home address is not questioned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory registration</td>
<td>Airplane, pencil, pine tree</td>
<td>Tree, car, hat</td>
<td>Tree, car, hat</td>
<td>Tree, car, hat</td>
</tr>
<tr>
<td>3 points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory recall</td>
<td>Tree, car, hat</td>
<td>Tree, car, hat</td>
<td>Tree, car, hat</td>
<td>Tree, car, hat</td>
</tr>
<tr>
<td>3 points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Attention and calculation | Only 100-7 (5 times), if unable to perform, the respondent is asked to say | Only 100-7 is questioned, 'saying a word backward' is left out due to the varying
| 5 points                  | 'sam cheon lee kang san' backward                                          | level of difficulty                                                        |                                                                            |                                                                            |
|                            | 'Clock, ballpoint pen                                                      |                                                                            |                                                                            |                                                                            |
| Language                  | 'Receive with the right hand / fold in half / put on the lap'              | 'Flip the paper over / fold in half / give it to me'                       |                                                                            |                                                                            |
| 8 points                  | Say repeat ‘gan jang jong jang kong jang jang jang’                        | Say repeat, 'Bak mu ni bul yeo ilkyun' . "up to twice, Writing of a simple sentence is asked |
|                            |                             <Reasoning><Judgment> tasks are offered instead of reading/writing |                                                                            |                                                                            |                                                                            |
| Visual construction       | Interlocking Pentagon copy                                                | Interlocking Pentagon copy                                                 | Interlocking Pentagon copy                                                 | Interlocking Pentagon copy                                                 |
| 1 point                   |                                                                            |                                                                            |                                                                            |                                                                            |

sam cheon lee kang san is a Korean idiom and means beautiful county. The 5 syllables substitute 5 items of 100-7

"gan jang jong jang kong jang jang is a kind of Korean tongue twister. It substitutes 'No ifs, ands, or buts'.

*** Bak mu ni bul yeo ilkyun is a Korean idiom and means 'seeing is believing'. It substitutes 'No ifs, ands, or buts'.

2. The Korean version of the Expanded Clinical Dementia Rating
Developed not as a screening tool for dementia but as an assessment tool for global cognitive and social
functions in Alzheimer disease (AD) patients, the Clinical Dementia Rating (CDR) has become one of the most commonly used scales to evaluate severity of dementia (Hughes et al, 1982; Morris et al, 1993). To cover a broad range of cognitive and social functions in patients with dementia, CDR is composed of 6 different domains of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. It is based on detailed interviews of both patients and care-givers. The expanded version using the 0-5 point scale has been translated and now in use in Korea (Choi et al, 2001). It can be administered by a trained nurse or neuropsychologist as well as physicians. McCulla et al reported that there was a high CDR score agreement between clinical nurse s and physicians (McCulla et al, 1989). Since CDR was developed to be used in AD patients, the items are heavily weighted toward memory decline, and the non-memory items also question functions whose impairment is mostly observed in AD. In this context, a study reported that CDR was not suitable for assessment of VaD or FTD characterized by early frontal lobe dysfunction (Padovani et al, 1995). It, however, is used for research purposes (Erkinjuntti et al, 2000) and for assessment of staging severity in all other dementia subtypes.

3. The Korean version of the Global Deterioration Scale

Like CDR, the Global Deterioration Scale (GDS) was developed to assess severity of degenerative dementia, not as a tool to screening of dementia (Reisberg et al, 1982). The difference is that GDS gives detailed cognitive descriptions elaborated with examples across varying stages of dementia, making it easier for raters to identify in which dementia phase the patient fits. It is also relatively quick. While patients with the same CDR score of 0.5 can still have different CDR-SB (sum of boxes) scores ranged 0.5 to 4.5, GDS stratification is 2 to 4, causing some to believe that GDS differentiates the earlier stages of dementia better than CDR. On the other hand, the CDR scores of 4 to 5 converge to the GDS 7 category, making GDS less sensitive to severe cognitive impairment. Developed for staging degenerative dementia, GDS also focuses heavily on memory decline, and is viewed relatively inappropriate to apply to VaD where frontal lobe dysfunction is manifested early. In reality, GDS is used for assessment of VaD severity in clinical studies (Fernandez-Novoa et al, 1997; Vetter et al, 1999). In Korea, it has been standardized and is of a wide use for early diagnosis and research of dementia (Choi et al, 2002).

4. Modified-MMSE

Modified-MMSE (3-MS) that seeks to compensate for the shortcomings of MMSE while maintaining its advantages has been standardized in Korea (Sohn et al, 2003). It has 4 additional subtests (date and place of birth, word fluency, similarities, and delayed recall) and a broader range of possible scores (0-100). When a cutoff score of 72 was used to diagnose dementia, the sensitivity and specificity was 73% and 74% respectively, and the age- and education-adjusted norms were presented. Compared with MMSE, 3-MS takes a longer time to administer.

5. Hasegawa Dementia Scale

Developed in Japan and used mostly in the eastern parts of the world, Hasegawa Dementia Scale
(HDS) has been standardized and used in Korea. It is less sensitive to the effects of age and education compared with the MMSE, contains items to test frontal functioning such as word fluency or counting backwards, and is useful for the elderly with visual or motor disturbances due to the absence of performance tasks. It is also applicable to the illiterate since the reading and writing requirement was excluded. In Korea, two standardized forms are currently available; K-HDS-R (Kang et al, 1999; Yang et al, 2004) and HDS-K (Kim et al, 2002). The two have different cutoff scores used for screening; ≤22/23 in K-HDS-R and ≤15/16 in HDS-K. The discrepancy, a possible limitation to clinical applicability, is attributable to the variability in the age and education levels of subjects and in the severity of dementia among standardization studies (Yang et al, 2004).

6. 7-Minute Screen Test

7-Minute Screen Test (7-MS) was developed by Solomon et al in 1998 as an easy and within-10-minute screening tool for early dementia. 7-MS is a compilation of the Benton temporal orientation test, enhanced cued recall, clock drawing, and category fluency. It is not influenced by the effects of age, gender, and education. It is easy and quick to administer even to non-professionals, and interpretable without expert knowledge. It showed a high sensitivity and specificity for mild AD as well as a high test-retest, inter-rater reliability, and was thus suggested as a valid screening tool for early AD (Solomon et al, 1998a, Solomon et al, 1998b). However, an education bias was observed in a domestic standardization in Korea (Park et al, 2002).

7. The Korean version of the Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) was developed to screen patients with mild cognitive impairment (MCI) who have normal MMSE findings (Nasreddine et al, 2005). The 30-point test assesses several cognitive domains including short-term memory, visuospatial abilities, executive functioning, attention/concentration/working memory, language, and orientation. Short-term memory is given 5 points, while visuospatial abilities are assessed using a clock drawing test (3 points) and a three-dimensional cube copy (1 point). Executive functions are assessed using the trail-making B task (1 point), a phonemic fluency task (1 point), and a 2-item verbal abstraction task (2 points). Attention is evaluated using a sustained attention task (1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Other tasks include animal naming (3 points), repetition of complex sentences (2 points), and orientation to time and place (6 points). In Korea, two standardized forms are currently available; MoCA-K (Lee et al, 2008) and K-MoCA (Kang et al, 2009). As seen with each item, the test involves more difficult tasks than MMSE for a better distinction of MCI. While the original MoCA cutoff for MCI was 25/26, the MoCA-K (Lee et al, 2008) uses a 3-point lower cutoff of 22/23, given the relatively small local elderly population with sufficient education. MoCA-K and K-MoCA show significant correlation with MMSE (r=0.65 in MoCA-K and MMSE-KC, r=0.85 in K-MoCA and K-MMSE).

C. Neuropsychological batteries

1. Neuropsychological batteries commonly used in Korea
(1) The Korean version of the CERAD Assessment Packets

The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) is a consultation organization of researchers from 16 major AD research centers in the US. Supported by the National Institute on Aging (NIA), it developed in 1989 the clinical and neuropsychological test batteries for evaluation of patients clinically diagnosed with AD (Morris et al, 1989).

First, the CERAD clinical assessment battery allows a systematic evaluation of patients aimed at collection of basic demographic data needed to establish a diagnosis. A clinical physician uses the assessment forms and guidelines provided in the battery to perform a series of tests such as semi-structured interviews of patients and carers, MMSE-KC, physical and neurological examinations, laboratory tests, and brain imaging (CT and/or MRI). Based on the obtained information, the clinician goes over the criteria provided in the battery and establishes the diagnosis of dementia accordingly. The developmental goal of the CERAD clinical assessment battery was to ensure a standardized diagnosis and evaluation of AD, but items were later added to cover non-AD dementias as well such as VaD, dementia with Lewy bodies (DLB), Parkinson’s disease dementia, and FTD.

Second, the CERAD neuropsychological assessment battery tests a broad range of dementia-related cognitive domains, with focus on the individual domains that tend to be consistently impaired in most AD patients. Those include memory, language, and visuospatial abilities. Considering the broad coverage of cognitive domain, the test is relatively quick (a total of 30-40 minutes), and easy to administer and score, thus useful for evaluation of older adults with dementia. The CERAD neuropsychological battery consisted of 7 subtests at the time of development in 1987. It was expanded in 1994 to have 8 tests (with addition of constructional recall) in the a-type packet for AD patients and 9 tests (with a further addition of the trail making test) in the b-type packet for non-AD dementia patients. With the depth of its contents, the CERAD neuropsychological assessment battery is widely used not only in the AD-related research organizations and hospitals in the US, but has been translated in 12 different languages and used in 40 or more countries including Korea for both research and clinical purposes.

In Korea, 12 dementia researchers from 9 healthcare institutions have gathered since 1995 to review the dementia assessment instruments. They had two objectives; to devise a tool that allows a standardized and systemized collection of diverse clinical information needed for diagnosis of dementia and to establish a neuropsychological test that allows a relatively brief but still comprehensive cognitive evaluation of patients with dementia. The English version of the revised CERAD battery (1994) was deemed the closest one for the above mentioned purposes. With it as a source document, the Korean Version of the CERAD Assessment Packet (CERAD-K) was developed (Lee et al, 2002). A simple word-to-word translation was avoided, while translational focus was given to word frequency (Seo SK, 1998), imagery, and the number of words and syllables in order to maintain the equivalence of the new battery as a diagnostic tool. The CERAD-K is structured that a physician could obtain history of patients with dementia in a systematic order. It showed a substantial inter-rater reliability and 1 month test-retest reliability. The Korean version of the Short Blessed Test (SBT-K) and MMSE-KC (Lee et al, 2002) also
showed a significant internal consistency.

1) Composition of CERAD-K

1. CERAD-K clinical assessment battery
   - It consists of the demographic data of subjects and informants, dementia-related clinical history, the Blessed Dementia Scale—Activities of Daily Living (BDS-ADL), MMSE-KC including SBT-K, physical and neurological examinations, laboratory tests and imaging, and CDR and diagnostic impression. Newly added items that were not part of the English CERAD battery are ‘present illness’, ‘family and personal history’, and ‘the Modified Hachinski Ischemic Scale (m-HIS)’ (Rosen et al, 1979).

2. CERAD-K neuropsychological assessment battery
   - It comprises 9 tests including verbal fluency (animal category), the shortened 15-item Boston Naming Test (BNT), MMSE-KC, word list memory, constructional praxis, word list recall, word list recognition, constructional recall, and the trail making test A & B. Administration takes 30~40 minutes (Table 1).

<table>
<thead>
<tr>
<th>Table 1. CERAD-K composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD-K clinical assessment battery</td>
</tr>
<tr>
<td>A Demographic data: subjects</td>
</tr>
<tr>
<td>B Demographic data: informants</td>
</tr>
<tr>
<td>C Clinical history</td>
</tr>
<tr>
<td>Present illness, personal and family history, clinical history, ADL (including BDS-ADL), screening for candidates for the BRSD, SBT-K, calculation, clock-drawing, and language expression</td>
</tr>
<tr>
<td>D Clinical examination</td>
</tr>
<tr>
<td>E Laboratory tests and imaging</td>
</tr>
<tr>
<td>F Clinical diagnosis</td>
</tr>
<tr>
<td>CERAD-K; the Korean Version of the Consortium to Establish a Registry for Alzheimer’s Disease Assessment Packet, ADL; Activities of Daily Living, BDS-ADL; Blessed Dementia Scale-ADL, BRSD; Behavioral Rating Scale for Dementia, SBT-K; Korean version of the Short Blessed Test, CDR; Clinical Dementia Rating, m-HIS the Modified Hachinski Ischemic Scale, BNT; Boston Naming Test, MMSE-KC; Mini-mental Status Examination.</td>
</tr>
</tbody>
</table>

(2) The Seoul Neuropsychological Screening Battery

The Seoul Neuropsychological Screening Battery (SNSB) was developed to discriminate among the domain-specific cognitive dysfunctions, to assess severity of dementia, to differentiate causes of dementia based on the cognitive manifestations, and to assess treatment effects in patients with dementia. A neuropsychological test in the evaluation of dementia needs a comprehensive assessment of diverse functions not only in the cognitive domains but in the affective, behavioral, and motor domains as well. At the same time, it needs to be short enough for older adults and patients with dementia, who easily get tired with a decreased attention span. Some of the established tests including MMSE, the Dementia Rating Scale, and the Neurobehavioral Cognitive Status Examination are strongly motivated toward a quick screening of dementia and thus innate with difficulty in delivering a comprehensive cognitive
assessments. SNSB was aimed at improving over the limitations of the earlier screening-focused tests and devised as a comprehensive and in-depth cognitive assessment tool that provides useful information for early diagnosis of dementia and determination of its causes.

SNSB, a comprehensive neuropsychological assessment battery, consists of multiple subtests to test a broad range of cognitive functions. The tests cover 5 cognitive domains: attention and concentration, language and related functions, visuospatial abilities, memory, and frontal/executive functions. Also included is K-MMSE, a widely used test for a brief global cognitive assessment and dementia screening, and the Geriatric Depression Scale, and Barthel ADL (B-ADL) to obtain information on how the emotional and physical status of a subject affects the cognitive functions assessed (Table 2). The SNSB neuropsychological tests are collected based on the following 3 criteria: 1) simple tests to instruct and administer with an improved applicability to the elderly, particularly those uneducated, 2) tests easy to implement at any places including the outpatient or inpatient unit, a public health center, or a senior community center with no fancy equipment except for a pen and the questionnaire, 3) tests having domestic standardization (K-MMSE, Korean version of BNT (K-BNT), Geriatric Depression Scale, B-ADL, and CDR). For tests that were included in SNSB but not standardized (the Seoul Verbal Learning Test (SVLT), the Korean-Color Word Stroop Test (K-CWST), and the Controlled Oral Word association Test (COWAT)), a separate standardization research has been done for their use in SNSB (Kang et al, 2003).

SNSB is a one-to-one test between a rater and subject. The subtests are arranged not by their belonging to a certain domain, but in a way that functions assessed in a test are not disturbed by another. To minimize the effect of subject fatigue, the tests deemed highly influenced by fatigue are deployed in the earlier part, while the ones relatively less subject to the fatigue effect are placed toward the end. The total test time is usually 1.5 to 2 hours. Though variable depending on the subject and environmental conditions, the developers of SNSB recommend a sequential test order presented below.


<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Neuropsychological Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Digit span: Forward / Backward</td>
</tr>
<tr>
<td></td>
<td>Letter cancellation</td>
</tr>
<tr>
<td></td>
<td>Spontaneous speech / Comprehension / Repetition</td>
</tr>
<tr>
<td></td>
<td>K-BNT</td>
</tr>
<tr>
<td></td>
<td>Reading / Writing</td>
</tr>
<tr>
<td></td>
<td>Finger naming / Right-Left orientation / Calculation</td>
</tr>
<tr>
<td>Language &amp; Related Functions</td>
<td></td>
</tr>
</tbody>
</table>
Body part identification
Praxis test: Buccofacial, Ideomotor
K-MMSE: Drawing
RCFT: Copy
K-MMSE: Registration / Recall

Visuospatial Functions
K-MMSE: Drawing
RCFT: Immediate & Delayed recalls / Recognition
Contrasting program / Go-No-Go test
Fist-Edge-Palm / Alternating hand movement
Alternating square & triangle / Luria loop

Memory
SVLT
COWAT
– Semantic (Animal, Supermarket)
– Phonemic (ㄱ, ㅇ, ㅅ)

Frontal/Executive Functions
Korean-Color Word Stroop Test (K-CWST)

Other Index
K-MMSE
Geriatric Depression Scale

B-ADL
CDR

SNSB; Seoul Neuropsychological Screening Battery, K-BNT; Korean version of the Boston Naming Test, K-MMSE; Korean version of the Mini-mental Status Examination. RCFT: Rey Complex Figure Test, SVLT Seoul Verbal Learning Test, COWAT; Controlled Oral Word Association Test, K-CWST; Korean-Color Word Stroop Test, B-ADL; Barthel Activities of Daily Living, CDR; Clinical Dementia Rating

1) SNSB-Dementia version
While SNSB is useful in providing comprehensive and in-depth cognitive information, it might be too lengthy for the fatigue-prone elderly or cognitively impaired patients. Furthermore, it doesn’t provide the global cognitive function (GCF) score useful for a longitudinal monitoring of patients. The SNSB-Dementia version (SNSB-D) was developed to address the limitations, using as reference a few neuropsychological tests that provide a GCF score including ADAS-cog, DRS, MMSE, and CERAD. SNSB-D provides a total GCF score of 300 distributed among attention 17 (6%), language & related function 27 (9%), visuospatial function 36 (12%), memory 150 (50%)-memory profiles are sub divided as orientation related 6 (4%), verbal memory 60 (40%) and visual memory 84(56%),and frontal lobe functions 70 (23%). Unlike the original SNSB, SNSB-D consists of only scorable tests. It sought be simple, choosing, for example, the 15-point shortened K-BNT in place of the 60-point full test. The frontal functions are also quantified, instead of the normal/abnormal assessment. In a preliminary study of the reliability and validity of the test involving 200 normal or ill subjects (MCI or dementia), the SNSB-D GCF score was shown as a valid and useful marker for discriminating among the normal, MCI, and dementia groups. It also had discriminant validity for the CDR staging of dementia severity. The internal consistency and test-retest reliability was all favorable (Jung, 2007, Ahn et al, 2010).

3) The Korean version of the Alzheimer’s Disease Assessment Scale
The Alzheimer’s Disease Assessment Scale (ADAS), originally developed by Rosen et al (1984), was designed to aid in the diagnosis of AD by assessing both cognitive and non-cognitive deficits characteristically observed in AD. The scale is made up of two portions; the 11-item cognitive portion (ADAS-cognitive subscale or ADAS-cog) and the 10-item non-cognitive portion (ADAS-non cognitive subscale). The ADAS-cog uses a 0 to 70 score range (and 0-50 in the non-cognitive portion). The lower the score, the better preserved the cognitive or non-cognitive functions.
The ADAS-cog is highly sensitive in screening early AD and assessing the progression of functional declines in patients with dementia. It is known as a very useful measurement of severity or staging of dementia. Performance is not influenced to the effect of education or age. In addition, the test has probably the most extensive reliability and validity studies available, conducted in different cultural regions (the Korean Association for Geriatric Psychiatry, 2003). With the advantages, the ADAS-cog has been used in a host of studies to assess the treatment effects of many anti-dementia drugs. It is also suggested as a standard evaluation tool for drugs that alter cognitive functions (Doraiswamy et al, 1997).

The original ADAS developed by Rosen et al has several limitations. First, the delayed recall in the ADAS-cog does not assess the non-verbal recall or ideomotor praxis, which are needed to detect an early cognitive decline and to improve the reliability. Attention is included in the non-cognitive portion, not in the ADAS-cog, making a lack of comprehensive assessment. Second, the word recognition task requires reading and memorization of 12 new words, different from the ones used in the word immediate recall, and recognition of the words out of a list that includes 12 interfering words. Some point out that the technique does not sufficiently evaluate the verbal storage. Lastly, the ADAS-cog does not include items to assess frontal dysfunctions, rendering it less sensitive in detecting a frontal variant of AD, or early FTD or VaD.

The Korean version of the ADAS (ADAS-K) was developed in 2002 by JC Youn et al. All the 21 items in the original English version by Rosen were kept and translated, with sufficient consideration given to the comparative word frequency and imagery (Youn et al, 2002). For standardization, its reliability and validity was assessed in a study involving 105 non-demented seniors and 84 patients with AD. The internal consistency was high, with a Cronbach’s $\alpha$ of 0.87. The value was also favorable at 0.88 with the ADAS-cog only. In the validity test, ADAS-K also showed a significant correlation with other neuropsychological assessment tools used for the diagnosis of dementia.

The ADAS-cog-K is also available in Korea (the Korean Association for Geriatric Psychiatry, 2003). The test covers 18 cognitive domains, including praxis abilities and frontal lobe functions that are left out in the original ADAS. Its clinical use, however, has only been eclectic, with only part of the test used as needed in clinical trials of several drugs.

**4) Severe Impairment Battery (SIB)**

While a number of neuropsychological assessment tools have been devised for the evaluation of cognitive functioning in patients with dementia, many of the earlier tests were aimed at measuring the presence and progression of cognitive impairment in patients with AD, particularly mild and moderate dementia, and were not accurate when applied to a severe dementia due to the floor effect. Their use in those with severe dementia has been further limited because of patient refusal or a gross cognitive worsening (Panisset et al, 1994; Schmitt et al, 1997).

Several attempts were made to compensate for the limitations associated with assessment of severe cognitive impairment; 1) use of the observation-based rating scales such as CDR and GDS for indirect evaluation in which clinical judgment is based on the information obtained from family members or friends.
and on the presence/absence of clinical symptoms, and 2) use of the Glasgow coma scale that evaluates neurological signs and symptoms and thus is without the floor effect. The alternatives also have been criticized, however, for the failure to provide performance-based cognitive information and the difficulty in assessing relatively intact cognitive domains. A series of neuropsychological tools have been developed to improve the shortcomings and is now used to assess severe cognitive impairment; the Severe Cognitive Impairment Profile, the Preliminary Neuropsychological Battery, the Test for Severe Impairment, and the Severe Impairment Battery (SIB) (Ahn et al, 2006). Of them, SIB is the most widely used across the world for reasons of easy administration and scoring as well as reasonable time consumption. Its standardization studies have been conducted in English, Italian, Spanish, French, and Swedish (Schmitt et al, 1997).

SIB, originally developed in 1990 by Saxton et al, consisted of 51 items under 9 assessment areas. It has a maximum score of 100 allocated to memory (0-14), language (0-46), orientation (0-6), visuospatial abilities (0-8), praxis skills (0-8), attention (0-6), construction (0-4), social interaction (0-6), and naming (0-2). Unlike the earlier neuropsychological tests, SIB uses one-word or short answer questions. The rater could use motions to help subject understanding, and repetition of the same question is allowed. Therefore SIB is well applied to severe dementia patients regardless of the level of communicative competence or education (Saxton et al, 1990; Nah et al 2006).

In Korea, two domestic versions have been verified for reliability and validity; the SIB for Korean population (SIB-K) (Ahn et al, 2006) and the Korean version of SIB (K-SIB) (Nah et al, 2006). SIB-K kept the original SIB framework, except for the minor changes; from reciting ‘the months of the year’ to ‘the days of the week’ and from ‘People spend money’ to ‘I bought something’. For verification of validity, it was compared with K-MMSE, CDR, and S-ADL. The spearman correlation coefficient was all favorable at 0.875, -0.678, and -0.661, respectively. The cutoff point was 62/63, with AUC 0.906, and both sensitivity and specificity were 88% (Ahn et al, 2006). K-SIB is a translation of the 3rd edition of SIB, revised and shortened in 1993. Validity was confirmed by evaluating the correlation with K-MMSE, CDR, CDR-SB, GDS, the Baylor Profound Mental Status Examination (BPMSE), B-ADL, K-IADL, and Functional assessment staging (FAST) (Reisberg, 1988). There was a high concurrent validity, with most of the correlation coefficients ≥0.5. The Cronbach’s α value, a marker of internal consistency, was 0.94, and the inter-rater reliability and intra-rater reliability was both significant at 0.51 and 0.99, respectively. In particular, of the severe dementia patients rated ≤10 by K-MMSE, the subgroup with a score 6 to10 showed a higher correlation with K-SIB (Na et al, 2006). Because of the insufficient research to the norm of the K-SIB norms, it is still unclear to conclude that K-SIB is a better reflection of the severe functional and cognitive impairment than K-MMSE. With a wider and more homogeneous score distribution compared with K-MMSE, it might be more useful for in-depth cognitive assessment and treatment planning in severely demented patients.

2. Other neuropsychological assessment batteries

(1) The Korean version of the Dementia Rating Scale
Aiming at accurate diagnosis of dementia and indexation of dementia progress, Chey et al developed and standardized the Korean version of the Dementia Rating Scale (K-DRS), by translating the original DRS by Mattis (1988) and making necessary revisions (Chey et al 1997; Park et al 1998). K-DRS was also to be used in local epidemiological surveys of dementia. Its clinical use for cognitive assessment in patients has been limited.

(2) Elderly Memory disorder Scale (EMS)

Elderly Memory disorder Scale (EMS) is a neuropsychological assessment battery that is mainly devoted to memory. It was developed to aid in the assessment of memory, visuospatial skills, language, and conceptualization in the Korean elderly population that has a large no-education group. EMS sought to improve over K-DRS and provide more detailed cognitive measurements, including the short form of the K-BNT developed by Kim HH (Kim HH et al, 1997) (Chei, 2006).
Recommendations

1. Cognitive assessment is essential to diagnosis and evaluation of dementia, and should be performed in all patients with dementia or suspected of dementia (Level A).
2. A comprehensive neuropsychological testing should be considered in all patients with non-severe dementia including prodromal dementia (Level C).
3. Cognitive assessment in patients with dementia should include a global cognitive measure and in addition more detailed testing of individual cognitive domains such as attention, memory, language, visuospatial abilities, executive functions, and instrumental functions (Level C).
References


Erkinjuntti T, Inzitari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, Roman GC, Chui H, Desmond DW.


Seo SK. The word frequency of current Korean based on a poll of Yonsei Corpus 1-9-frequency 7 or more. Yonsei Institute of Language and Information Studies, Seoul, 1998.


Vetter PH, Krauss S, Steiner O, Kropp P, Möller WD, Moises HW, Köller O. Vascular dementia versus


Chapter 4. Behavioral and Psychological Symptoms of Dementia and Activities of Daily Living

A. Behavioral and psychological symptoms of dementia

1. Behavioral and psychological symptoms of dementia in patients with dementia

The diagnosis of dementia is focused on the cognitive functions including memory, language, visuospatial abilities, calculation, conceptual or semantic knowledge, and executive functions. However it is well known that patients with dementia present behavioral disturbances and other psychological symptoms in addition to the cognitive symptoms. Various terms have been used to describe the behavioral disturbances commonly observed in dementia, some of which include ‘behavioral disturbances of dementia’, ‘non-cognitive symptoms of dementia’, ‘neuropsychiatric symptoms of dementia’, ‘psychiatric symptoms and behavioral psychopathology of dementia’, ‘behavioral problems of dementia’, and ‘problem behaviors of dementia’ (Han, 2004). The International Psychogeriatric Association (IPA) agreed to address all the non-cognitive symptoms in dementia as ‘behavioral and psychological symptoms in dementia’ or BPSD (Finkel et al, 1996). IPA defined BPSD as ‘symptoms of disturbed perception, thought contents, mood, or behavior that frequently occur in patients with dementia’. Until the early 1990s, they were viewed as secondary to cognitive impairment or comorbidity and not as a major symptom of dementia. There are reports, however, that behavioral disturbances and psychiatric symptoms develop independently in dementia, not secondary to memory or cognitive impairment. They are supported by the observation that BPSD is in the moderate stage of dementia, whereas cognitive symptoms start early and continue to worsen along the disease course (Shinosaki et al, 2000). Others have come to think that BPSD has a different developmental mechanism from cognitive impairment, a hypothesis that grew with the methodological advance in neuroscience and subsequent proliferation of the neuropsychological, neurochemical, psychophysiological studies of BPSD.

BPSD manifestations are determined mainly affected brain region or circuits rather than causes of dementia (Table 1) (Cummings, 2003).

<table>
<thead>
<tr>
<th>BPSD</th>
<th>Affected Brain Regions or Circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania</td>
<td>right inferomedial cortex, caudate nucleus, thalamus, temporal-thalamic projection</td>
</tr>
<tr>
<td>Depression</td>
<td>left anterior frontal cortex, left caudate (in the acute post-stroke period)</td>
</tr>
<tr>
<td>Psychosis with first-rank symptoms</td>
<td>left temporal cortex</td>
</tr>
<tr>
<td>Psychosis with misidentification</td>
<td>right hemisphere</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>orbital or medial frontal cortex, caudate nucleus, globus pallidus</td>
</tr>
<tr>
<td>Apathy</td>
<td>anterior cingulate gyrus, nucleus accumbens, globus pallidus, thalamus</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>orbitofrontal cortex, hypothalamus, septum</td>
</tr>
</tbody>
</table>
Earlier studies have reported that BPSD is found in approximately 70-95% of the facility-based elderly with dementia (Ballard et al, 2001; Rovner et al, 1986) and 60% of the home-based elderly with dementia (Lyketsos et al, 2000). The types of BPSD in the order of descending frequency include agitation, abnormal eating behaviors, affective disorders/mood disturbances, incontinence, delusions, Kluver-Bucy syndrome, hallucinations, anxiety-phobia-fear-illusions, shouting/screaming, restlessness, demanding/critical behavior, wandering, personality change, rage/violence, disinhibition, sleep-awake disturbances, sexual behaviors, sundowning, and obsessive-compulsive behaviors (Rapp et al, 1992).

The clinical significance of BPSD grows for the following reasons; first, BPSD is the biggest cause of early institutionalization of the patients with dementia. It deteriorates the quality of life for family members and further aggravates the patients' disabilities. Second, BPSD increases the cost of patient care. In the US, the yearly cost of care per Alzheimer disease (AD) patient is estimated at 25,000~30,000 USD, a big portion of which incurs due to BPSD (Finkel, 2000). Third, compared with cognitive symptoms, BPSD has much for symptomatic improvement with pharmacological or non-pharmacological interventions. If detected and treated appropriately, BPSD is more amenable to treatment than cognitive impairment, leading to a greater improvement in the quality of life for patients and care-givers (Han, 2004). In a domestic study of BPSD in the nursing home patients with dementia, the least prevalent NIP-Q item was apathy/indifference (33%) as opposed the most prevalent of agitation/ aggression (59%) (Shim et al, 2005).

The most common classification of BPSD is to divide them into behavioral and psychological symptoms. Psychological symptoms include delusion, hallucination, paranoia, depression, anxiety, reduplication, and misidentification. Behavioral symptoms are aggression, wandering, sleep disturbances, inappropriate eating behaviors, and inappropriate sexual behaviors. They are often further categorized by severity into Group 1, 2, or 3 (Luxenberg, 2000). Group 1 includes psychological symptoms of delusion, hallucination, depression, insomnia, and anxiety, aggression, wandering, and restlessness. Group 2 has a psychological symptom of misidentification and behavioral symptoms of agitation, disinhibition, culturally inappropriate behaviors, and shouting. Group 3 includes only behavioral symptoms of crying, cursing, apathy, repetitive questioning, and shadowing (Table 2).

**Table 2. BPSD classification by frequency and the degree of distress (Luxenberg, 2000)**

<table>
<thead>
<tr>
<th>Psychological BPSD</th>
<th>Behavioral BPSD</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>delusion, hallucination, depression, insomnia, anxiety</td>
<td>aggression, wandering, restlessness</td>
<td>misidentification</td>
<td>agitation, disinhibition, culturally inappropriate behaviors, shouting</td>
<td>crying, cursing, apathy, repetitive questioning, shadowing</td>
</tr>
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</table>

BPSD means Behavioral and Psychological Symptoms of Dementia.
Specific descriptions of each symptom are provided below. Of the psychological symptoms, delusion is a false belief based on incorrect inference about an external reality. It is irrelevant to the person's education level or environment, and not corrected by rational and logical explanations. Unlike delusion in schizophrenia, delusion in dementia is uncomplicated and unspecific with its contents frequently changing (Cummings, 1985). Delusion develops along the disease course in about 50% of AD patients (Mendez et al, 1990), its prevalence particularly high in the moderate stage of dementia and decreasing as the disease advances (Mendez et al, 1987). Delusion of theft is the most common type (18-43%), followed by delusion of abandonment (3-18%), and delusion of infidelity (1-9%) (Luxenberg, 2000). In vascular dementia (VaD), particularly multi-infarct dementia, about 40-50% of patients have delusion which tends to show a similar pattern as in AD and irrespective of the MMSE scores (Cummings et al, 1987).

Hallucination is defined as a sensory perception in the absence of external stimuli, which has qualities of real perception. Though less common than delusion, hallucination is reported in 12-49% of patients with dementia. Visual hallucination is found in 15% of patients with AD and auditory hallucination in 12%. The prevalence of hallucination in AD patients varies widely among studies, with visual hallucination generally more common than auditory types (Mendez et al, 1990). Hallucination is known to be more frequent in multi-infarct dementia than in AD. It accelerates the cognitive decline and increases the risk of aggressive behaviors, affecting the prognosis of dementia (Forstl et al, 1993; Gormley et al, 1998).

Depression develops in about 40-50% of AD patients (Burns et al, 1990), though the one with a diagnostic significance is found in 10-30% (Reding et al, 1985; Teri and Wagner, 1991). There are reports that dementia developed 3 to 8 years after the onset of depression in 40-91% of the depressed elderly patients who didn't have dementia at the onset of depression (Kral and Emery, 1989; Reding et al, 1985). Another natural history study of 100 autopsy-confirmed AD patients revealed that they experienced depression 26 months before the diagnosis of AD (Jost et al, 1996). Based on the reports, some suggest that depression is a prodrome of AD (Hwang et al, 2004). The prevalence of depression in dementia are known to be irrespective of the severity of dementia, patient's self awareness of illness, or care-giver mood (Cummings et al, 1995).

Depression is more common in multi-infarct dementia than in AD (Cummings et al, 1987; Reding et al, 1985). In a study of patients with AD or multi-infarct dementia, a depression prevalence of 17% was found with the Hamilton depression scale in the AD patients, though none was severe enough to meet the diagnostic criteria of major depression. As mentioned earlier, depressive disorder frequently develops along the course of dementia, while cognitive dysfunction is common in major depression. Clinical differentiation between the two is important, but hindered in reality for several reasons. First, in patients with dementia, symptoms such as psychomotor retardation, emotional fluctuation, sleep disturbance, weight loss, reduced emotional expression, and pessimistic thoughts are common in the absence of depression. Furthermore, apathy, one of the hallmark characteristics of dementia, is frequently reported as depression by care-givers (Mackenzie et al, 1989). Second, detection of depression disorder in older adults is difficult even for experienced clinicians. Depression in the elderly is characteristically addressed
'depression without sadness', and the elderly with depression tend to report less affective symptoms compared with younger patients (Gallo and Rabins, 1999). Patients with dementia often lack the ability to make consistent self-reports, and they tend to underestimate their affective symptoms (Teri and Wagner, 1991).

Apathy is the most frequently observed BPSD in the patients with dementia. It refers to diminished motivation and goal-directed behaviors. Apathy may have affective, emotional, cognitive, and behavioral manifestations. Affective apathy manifests as lack of empathy or inertia. Emotional changes include indifference to the surroundings or loss of interest. Cognitive changes are decrease in productive thinking, loss of curiosity and attention, and reduced involvement in daily activities. From the behavioral aspects, the apathetic patients are indolent, less productive, find it difficult to initiate physical activities or maintain certain behaviors (Cummings, 2003).

Anxiety is common in dementia, and associated with irritability, aggression, psychomotor agitation, and helpless weeping. Symptoms such as pacing, chanting, or repetitive tapping might be caused by underlying anxiety. Refusal of bathing, dressing, tooth-brushing, or feet-washing might be a result of situational anxiety that fears a sudden change in situations. Anxiety might also develop from the fear of being left alone or as one of the symptoms of depression (Luxenberg, 2000).

With regard to behavioral symptoms in BPSD, aggression is one of the most commonly complained about by care-givers (Nagaratnam et al, 1998). It is manifested physically and/or verbally (Cohen-Mansfield et al, 1996). Physically aggressive behaviors include hitting, pushing, grabbing, kicking, and biting, while verbally aggressive behaviors comprise screaming, cursing, and temper outburst. Irritability and aggressive behaviors are shown in 30-50% of AD patients.

Wandering is a serious behavioral symptom that could threat to the safety of patients. Its prevalence in AD is approximately 53%. While wandering is used as a clinical term in AD, it is also used as a descriptive term for a heterogeneous group of behavioral symptoms. The definition of wandering has been inconsistent in studies and is not clearly established yet, but the most useful one seems to be ‘a tendency to move about in either the seemingly aimless or disoriented fashion or in pursuit of an indefinable or unobtainable goal’ (Snyder, 1978). Wandering is a significant source of distress for care-givers, being one of the major symptoms for which patients are brought to or admitted to facilities or hospitals. Compared with VaD, patients with AD are more likely to get lost outside of their houses, but that was not correlated to the degree of wandering or cognitive impairment (Ballard, 1991). Symptoms of wandering are often classified; checking/trailing, pottering, aimless walking, walking with inappropriate purpose, walking with appropriate purpose but inappropriate frequency, excessive activity, night-time walking, needs to be brought back home, and attempts to leave home (Ballard, 1991).

Repetitive behaviors are observed in many AD patients. Some patients might just continue walking once they start without aims or targets. Others might not stop clapping or folding/unfolding the laundry.

Other behavioral symptoms include inappropriate eating behavior, inappropriate sexual behavior, and rage reaction.
Assessment of BPSD is recommended essential for diagnosis and treatment of dementia (EFNS, 2007). Information should be aggressively gathered from informants who know the patient well using an appropriate rating scale. BPSD often have somatic comorbidity or complications including cardiovascular disease, infection, drug adverse events, delirium, falls, incontinence, and anorexia. The comorbidity might cause a rapid cognitive decline in dementia. Treatment of BPSD should also cover a possible causative somatic comorbidity or complication (EFNS, 2007).

2. Instruments for BPSD assessment

Evaluation of aberrant behaviors in dementia is important for the following reasons.

First, aberrant behaviors or personality change might represent early symptoms of dementia, prodromal to cognitive impairment (Petry et al, 1988; Rubin and Kinscherf, 1989). Their assessment is important in the diagnostic context. Second, aberrant behaviors are a major source of distress for care-givers, and a cause for institutionalization in patients with dementia. Since BPSDs are controllable with variable pharmacological or non-pharmacological interventions to a great degree, accurate assessment is essential for the treatment purpose as well. Meanwhile, abnormal behaviors don’t show a steady progress as with cognitive impairment such as memory, but their types change along the course of dementia. Re-evaluation is needed for determination of treatments for specific symptoms. Third, aberrant behaviors are a major prognosis factor, and cognitive decline is rapid if delirium or hallucination exists (Lopez et al, 1991; Mortimer et al, 1992; Stern et al, 1987). Fourth, improvement in aberrant behaviors is used as an important measure of the effects of newly developed anti-dementia medications. Appropriate assessment of aberrant behaviors before and after treatment with use of the appropriate tools is critical.

There are several tools used for assessment of abnormal behaviors in dementia; BEHAVE-AD (Reisberg et al, 1987), the California Dementia Behavior Questionnaire (Victoroff et al, 1997), the Neurobehavior Rating Scale (Levin et al, 1987), the Columbia University Scale for Psychopathology in Alzheimer’s disease (CUSPAD) (Devanand et al, 1992), the Cornell Scale for Depression in Dementia (Alexopoulos et al, 1988), the Neuropsychiatric Inventory (NPI) (Cummings et al, 1994), and the Behavior Rating Scale for Dementia (BRSD) of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) (Tariot et al, 1995). Of them, NPI, BEHAVE-AD, and BRSD have been translated into Korean and standardized (Choi et al, 2000; Suh et al, 2001; Youn et al, 2008).

The NPI was developed by Cummings et al (1994) aiming at evaluation of behavioral disturbances in patients with dementia or other diseases. The NPI tests 12 aberrant behaviors including delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, night-time behaviors, and appetite/eating changes. The NPI consists of screening questions and subquestions. Raters interview caregivers who know the patient well and assess the severity, frequency, and the degree of caregiver distress for each behavioral item. Internal consistency of the test was a Cronbach’s α value of 0.85. The test-retest reliability was 0.63 (p<0.001) for the frequency, and 0.64 (p<0.001) for the severity. Variations of NPI include NPI-Q, a more convenient version to be used in the clinical settings, and NPI-NH, a nursing home
version used to assess aberrant behaviors in the facility residents with dementia.

Caregiver-administered (CGA)-NPI was devised to reduce the test administration time (Kang S.J., 2004). It is not an interview-based test, but uses a questionnaire to be read and answered by caregivers themselves. Other than that, the test bears much similarity to the original NPI. CGA-NPI was significantly correlated to NPI for all 12 items included ($r=0.58-0.89$).

BEHAVE-AD mainly consists of behavioral items in AD that are a significant source of distress for caregivers and are treatable with drugs or other therapy (Reisberg et al, 1987). A rater questions caregivers who know the patient's illness well to assess aberrant behaviors present over the past 2 weeks. BEHAVE-AD contains two parts. In part 1, a total of 25 symptoms in 7 clusters are rated: paranoid and delusional ideation, hallucination, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties and phobias. Part 2 is a global rating of caregiver distress caused by the specific symptoms; the caregiver determines a level of distress on a 0-3 scale. The test has been translated into Korean and verified (Suh et al, 2001).

In 1992, BRSD was developed out of the large CERAD initiative (Tariot et al, 1995). The original version contained 48 items, of which 2 items were left out later to create a 46-item BRSD in 1996. It was also translated into Korean and standardized (Suh, 2003). The test assesses a patient's aberrant behaviors over the past month based on a caregiver interview. Since most of the items question presence/absence of a specific behavior, regardless of the time of onset of dementia or progression status, that particular behavior is counted even if it is not related to dementia or had lasted lifetime. A factor analysis identified 8 factors of BRSD; depressive features, psychotic features, defective self-regulation, irritability/agitation, vegetative features, apathy, aggression, and affective lability. The inter-rater reliability ranged 0.866 (vegetative symptoms) to 0.966 (psychotics symptoms) ($p<0.01$), and the test-retest reliability was high, ranging from 0.780 (inertia) to 0.982 (total weighted score).

B. Activities of Daily Living (ADL)

1. ADL in patients with dementia

ADL is a measure of a person's ability to live independently. The independent ADL implies that the person can perform the basic activities needed for personal care and the more complex activities needed to maintain a social life without help. ADL is largely classified into physical (P-ADL) and instrumental (I-ADL). P-ADL measures basic physical functions including bowel/bladder continence, toilet use, grooming, bathing, feeding, dressing, transfers, mobility, and climbing stairs (Mahoney and Barthel, 1965). I-ADL measures more complex functions: telephone use, shopping, meal preparation, handling money and other financial matters, housework, using transportation and finding directions, hobbies, taking medications, reading, laundry, leisure activities like watching TV, inquisitive-creative activities, and situational response (Hindmarch et al, 1998; Lawton and Brody, 1969). Assessment of I-ADL in dementia is important for the following reasons. First, IADL assessment is needed to establish diagnosis of dementia, whose diagnostic criteria include significant disturbances with activities of daily or social living.
as well as cognitive impairment. Second, I-ADL assessment aids in the early diagnosis of dementia (Rubin et al., 1989). In degenerative dementia such as AD, P-ADL is maintained to the later stages of dementia, while I-ADL shows an early decline (Juva et al., 1997). Third, I-ADL improvement is an important measure of the effect of anti-dementia medications (Galasko et al., 2004). Fourth, I-ADL assessment allows healthcare professionals to obtain and use for treatment detailed information on how independently the patient maintains daily living (Rubin et al., 1989). ADL should be assessed in patients for diagnosis of dementia (EFNS, 2007).

2. Instruments for ADL assessment

ADL is assessed either by enquiry or use of established tools whose reliability and validity have been verified. For enquiry, a physician needs to ask a patient or caregiver about the patient's daily routines, for example, what he or she does to spend a day after waking up in the morning. Specifically, the physician questions if the patient can wash, feed, use toilet, bathe, dress, walk, or transfer themselves independently, or with assistance, or is unable to perform these tasks. More complex activities such as use of the telephone, shopping, meal preparation, money handling, housework, use of transportation, finding directions, hobbies, and reading should also be questioned to see if a previous level of independence is maintained, or assistance is needed, or they can't be performed.

There are several ADL assessment tools used in Korea; the Korean version of IADL (K-IADL) (Kang et al., 2002), the Korean version of the Bayer ADL (B-ADL) (Choi et al., 2003), the Korean version of the Disability Assessment for Dementia scale (DAD) (Suh et al., 2003), the Seoul-activities of daily living (S-ADL) (Koo et al., 2004a), the Seoul-instrumental activities of daily living (S-IADL) (Koo et al., 2004b), and the modified Barthel index.

K-IADL, a modified and translated version of Lawton's ADL, evaluates a patient's abilities over the past 4 weeks using 11 I-ADL items of grocery shopping, mode of transportation, ability to handle finances, housekeeping, preparing food, ability to use a telephone, responsibility for own medication, recent memory, hobbies, watching TV, and fixing around the house. The test uses easy-to-understand sentences, and adds 'Not Applicable' as an answer considering gender and cultural difference. For scoring, a mean score of the items is calculated excluding the ones marked with 'Not Applicable' items.

In the test-retest of K-IADL, all the 11 items showed a significantly high correlation: shopping (r=0.95, p<0.001), mode of transportation (r=0.94, p<0.001), ability to handle finances (r=0.87, p<0.001), housekeeping (r=0.82, p<0.001), preparing food (r=0.94, p<0.001), ability to use a telephone (r=0.90, p<0.001), responsibility for own medication (r=0.75, p<0.001), recent memory (r=0.87, p<0.001), hobbies (r=0.81, p<0.001), watching TV (r=0.83, p<0.001), and fixing around the house (r=0.65, p<0.05). The global score also showed a statistically significant correlation (r=0.94, p<0.001). In the internal consistency reliability test, the average inter-item correlation was 0.67, with the individual correlations maintained in a stable range. The average item total correlation was 0.79, and Cronbach's α value was 0.96, suggesting a high internal consistency. The area under the ROC curve, a marker of
performance of a screening test, was 90.3% (Standard Error=2%). When a cutoff score of 0.43 was used, sensitivity was 83%, and specificity was 82%.

The Bayer ADL was developed through an international research involving the US, Germany, Britain, Russia, and Greece (Hindmarch et al, 1998). It has been translated into Korean, and the reliability and validity have been verified (Choi et al, 2003). The tool provides a 10-point scale, useful for documentation of treatment effects. It also includes the I-ADL items whose performance decline is prominent in early dementia, thus is sensitive to early IADL impairment. The test consists of 25 items assessing performance over the past 4 weeks. The test-retest agreement was 0.95 (p<0.001), and Cronbach’s α value was 0.982, showing a high internal consistency.

The Korean version of the Disability Assessment for Dementia scale (DAD-K) assesses 10 domains including P-ADL (personal hygiene, dressing, continence, eating), I-ADL (meal preparation, telephoning, going on an outing, finance and correspondence, medications), and leisure activities (leisure and housework). Individual items are assessed against 3 standards; initiation, planning and organization, and effective performance. Assessment is based on the patient’s actual performance observed over the 2 weeks prior to the interview.

The Seoul-Activities of Daily Living (S-ADL) is based on the Barthel ADL items, but factored in clinical experiences and cultural difference in Korea. To the 10 Barthel ADL items, 2 items of ‘being left alone’ and ‘shoe wearing’ were added, and each item was assessed on a simplified 0-2 scale. The internal consistency of S-ADL was 0.90, and the inter-rater agreement was 0.654-1.000 (p<0.001).

As with S-ADL, the Seoul-Instrumental Activities of Daily Living (S-IADL) has been tailored to the cultural characteristics of Korea. IADL is assessed against ‘current performance’ and ‘potential performance’. S-IADL selected 15 items from the usual IADL items, and adopted a 0-3 scale rating. It compensated for the limitation of excluding the items marked ‘Not Applicable’ from evaluation, as in K-IADL. The assessment focus was on current performance, improving the inter-rater agreement. The area under the ROC curve, a measure of diagnostic accuracy, was 95.6% (standard error=1.4%, p<0.001). When a cutoff point of 8 was used, sensitivity (the proportion of actual positives correctly identified as having dementia) was 83.3%, and specificity (the proportion of actual negatives correctly identified as not having dementia at 7 and lower) was 93.1%. The internal consistency was 0.94, and the test-retest reliability was 0.63(p<0.001). The inter-rater agreement was 0.552~0.811 (p<0.001).

The Modified Barthel Index is a P-ADL assessment tool widely used in Korea. The test assesses the current performance level for each itemized physical activity, regardless of whether a P-ADL decline has a cognitive origin or a physical origin such as stroke.
Recommendations

1. Assessment of behavioral and psychological symptoms of dementia is essential for both diagnosis and management, and should be performed in all patients (Level A).

2. Behavioral and psychological symptoms often have somatic co-morbidity or complications. A possible causative co-morbidity or complication should be included in evaluation (Level A).

3. Activities of daily living (ADL) should be assessed in all patients for diagnosis of dementia (Level A).

4. Assessment of ADL should include both the physical and instrumental fields (Level A).
References


Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and


Shim YS, Kim BS, Shon YM, Kim KS, Yoon BR, Yang DW. Clinical Characteristics of Demented Patients in a Geriatric Institution: Focused on Behavioral and Psychological Symptoms Dementia and


Chapter 5. Laboratory Tests of Dementia

A. Objectives of the laboratory tests in the diagnostic workup of dementia

Laboratory screening with blood tests is recognized as an integral part of the general screening of a patient presenting with cognitive disturbances. The aims of blood tests include (1) identification of co-morbidity and/or complications, (2) revealing potential risk factors, (3) exploration of background medical conditions frequently associated confusional states, and (4) in rare cases, identification of the primary cause of dementia.

Cognitive disturbances may be associated with a wide range of metabolic, infectious, and toxic conditions. For most of these conditions, however, there is no specific evidence from randomized clinical trials that treatment will reverse cognitive symptoms (Clarfield, 2003). Yet, a specialist physician is often dealing with patients with confusional states, rapid progression or atypical presentation, in whom blood tests may be of diagnostic and treatment value.

B. Blood tests in the diagnostic workup of dementia

The following blood tests are generally recommended as mandatory tests for all patients at first evaluation: blood sedimentation rates, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating hormone. More extensive tests will often be required (vitamin B12, folate levels, and serological tests for syphilis, human immunodeficiency virus (HIV), and Borrelia) in individual cases. Tests for HIV are not routinely performed in patients suspected of dementia. It should only be considered in patients who have clinical manifestations or medical history that increases the risk of HIV infection (Psychiatrists, 2005). Mid-stream urine test should be performed if delirium is a possibility.

C. Cerebrospinal fluid analysis in the diagnostic work-up of dementia

Cerebrospinal fluid (CSF) testing is recommended in patients with a clinical suspicion of certain diseases and in patients with atypical clinical presentations. Examination of CSF (with routine cell count, protein, glucose, and protein electrophoresis) is mandatory if inflammatory disease, vasculitis, or demyelination is suspected as a cause of dementia, though not recommended as a routine test. The CSF levels of total tau protein, phospho-tau, and β-amyloid can be used as an adjunct if there is diagnostic doubt (Andreasen et al, 2005) (Level B). In rapidly progressive dementia, the 14-3-3 protein test is recommended to identify Creutzfeldt-Jacob disease (CJD) (Hsich et al, 1996) (Level B).

D. β-amyloid and phospho-tau in cerebrospinal fluid

A large body of literature has emerged investigating the added value of specific biomarkers in CSF such as β-amyloid 1-42 (Aβ42), total tau (tau), phospho-tau, and the 14-3-3 protein. Aβ42 is decreased in the CSF
of Alzheimer disease (AD) patients possibly as a result of the deposition of fibrillar Aβ42 in senile plaques. Tau is increased in the CSF of AD patients, as reflection of the release of tau in CSF with neuronal loss (Blennow et al, 2003a; Blennow et al, 2003b; Sunderland et al, 2004). Phospho-tau derives from tangle deposition. The presence of the 14-3-3 protein in CSF is a measure for acute neuronal loss and brain damage and is associated with CJD (Hsich et al, 1996).

1. Alzheimer’s disease versus controls

Aβ42 is decreased and tau increased in the CSF of AD patients compared to non-demented controls, patients with depression, and patients with memory complaints on the basis of alcohol abuse (Blennow et al, 2003a; Blennow et al, 1995; Sunderland et al, 2004). The pooled sensitivity and specificity for Aβ42 in AD versus controls from multiple studies was 86% and 90%. For tau, the sensitivity was 81% and the specificity 90%. A recent meta-analysis showed a considerable inter-laboratory difference in the absolute concentrations of β-amyloid and tau, even when the same test kit was used. Using a combination of both markers for AD versus controls, a high sensitivity (85-94%) and specificity (83-100%) can be reached (Verbeek et al, 2003). In patients with early onset AD compared with controls, a sensitivity of 81% with specificity of 100% was found. In two studies that had neuropathological validation of the diagnosis, the same high sensitivity and specificity for the distinction of AD from controls was found (Tapiola et al, 2000). One study investigated and found an association between the number of senile plaques and concentration of β-amyloid in CSF (Strozyk et al, 2003).

2. Alzheimer’s disease versus other dementias

A decreased level of CSF- β-amyloid is found in fronto-temporal dementia (FTD), dementia with Lewy bodies (DBL), and CJD when compared with controls (Hulstaert et al, 1999; Kanemaru et al, 2000; Nagga et al, 2002; Riemenschneider et al, 2002; Van Everbroeck et al, 1999; Van Everbroeck et al, 2003). Tau is increased in many other dementias such as FTD (Fabre et al, 2001; Green et al, 1999) and CJD (Otto et al, 2002). In vascular dementia (VaD), conflicting results have been reported; specificity varied between 14% and 83% compared with AD (Andreassen et al, 1998; Blennow et al, 2003a; Blennow et al, 1995; Kapaki et al, 2003). In FTD, specificity varied from 26% to 75%. In DLB, tau is usually normal. The combination of β-amyloid and total tau increases specificity and the negative predictive value: AD versus total group other dementias; 58-85%; AD versus FTD: 85%; AD versus DLB and VaD specificity 67% and 48%, respectively, with a negative predictive value of 95%. Alzheimer’s disease compared with an age-matched FTD group yielded good sensitivity (72%) and specificity (89%) and a very low negative likelihood ratio. In general, for studies in which phosho tau was added, specificity was even higher.

3. Creutzfeldt-Jacob disease

In CJD, tau levels were higher than in AD, yielding a high sensitivity (93%) and specificity (90–100%). Assessment of the 14-3-3 protein in the sporadic form of CJD has a sensitivity of 90–100% and a specificity of 84–96% (Lemstra et al, 2001; Lemstra et al, 2000; Van Everbroeck et al, 1999; Van Everbroeck et al, 2003; Zerr et al, 1998; Zerr et al, 2000). False positives can be found in cerebral infarcts,
encephalitis, tumors, and rapidly progressive AD. When clinical suspicion of CJD is high, the combination of electroencephalogram, MRI, and 14-3-3 assessment increases the accuracy (Lemstra et al, 2000).

E. Genetic testing in the diagnostic workup of dementia

Many degenerative dementias occur as autosomal dominant disorders with similar phenotypes to sporadic disease apart from an earlier age at onset. The prevalence of autosomal dominant disease varies from <1% in AD to nearly 50% in some series of FTD. Three causative genes have been identified in familial AD; the amyloid precursor protein (APP) gene and the presenilin 1 and 2 genes. Tau mutations are found in some cases of familial FTD and mutations in the prion protein gene in familial CJD. The yield of a mutation screening in a group clinically diagnosed with non-Alzheimer dementias is low (Houlden et al, 1999). However, with an appropriate phenotype and an autosomal dominant family history, gene testing for known mutations can provide a specific diagnosis. The identification of a known pathogenic mutation in an affected family member can permit pre-symptomatic testing, and in this case, the Huntington’s disease protocol for predictive testing and counseling should be followed (Harper et al, 1990).

A variety of risk genes have been identified, and the most carefully studied is apolipoprotein E (Apo E) allele polymorphism. The addition of Apo E testing increased the positive predictive value of a diagnosis of AD from 90% to 94% in a neuropathologically confirmed series (Mayeux et al, 1998). In patients with a clinical diagnosis of non-Alzheimer dementia, the absence of an Apo E₄ allele increased the negative predictive value from 64% to 72%.

F. Biopsy in the diagnostic workup of dementia

Cerebral biopsy can provide a specific histological diagnosis, but should only be undertaken when a treatable disorder is considered, such as cerebral vasculitis. In general, a non-dominant frontal or temporal pole full thickness biopsy to include leptomeninges and white matter should be performed. If a prion disease is suspected, it can not be excluded from the differential diagnosis, and either disposable craniotomy instruments should be used, or they should be quarantined until a final diagnosis has been made.

G. Other investigations in the diagnostic workup of dementia

Additional investigations may provide critical information in the differential diagnosis of dementia, including metabolic studies from fibroblast cultures, white cell enzyme assays, and urinary amino acids. Biopsies of specific tissues might be invaluable, for example, liver biopsy in Wilson’s disease, and skin and muscle biopsies in conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (100% specificity and 45% sensitivity) (Markus et al, 2002),
Lafora body disease, and mitochondrial cytopathy. Tonsilar biopsy can demonstrate the presence of prion protein in variant CJD.
## Recommendations

1. The following laboratory tests should be performed in the evaluation of patients with dementia: CBC, blood sedimentation rate, electrolytes, calcium, glucose, renal and liver functions, thyroid functions, vitamin B₁₂, folic acid, syphilis, human immunodeficiency virus, and urinalysis (Level B).

2. CSF analysis should be performed in patients when there is clinical suspicion of certain diseases and in patients with atypical clinical presentations (Level B).
   
   A. Examination of CSF (with routine cell count, protein, glucose, and protein electrophoresis) is mandatory if inflammatory disease, vasculitis, or demyelination is suspected as a cause of dementia.
   
   B. CSF total tau, phospho tau, and β-amyloid (Aβ₄₂) should be used as an adjunct in cases of diagnostic doubt.
   
   C. For the identification of Creutzfeldt-Jacob disease in cases with rapidly progressive dementia, assessment of the 14-3-3 protein should be performed.

3. The genetic testing of dementia should be restricted to the following cases. They must only be undertaken with consent from the patient and caregivers (Level B).
   
   A. A patient with an appropriate phenotype and a family history of autosomal dominant dementia

   B. An asymptomatic adult individual with a clear family history of dementia when there is a known mutation in an affected family member to ensure that a negative result is clinically significant.

4. Routine Apo E genotyping in all patients with dementia is not recommended (Level B).

5. Biopsy should only be undertaken at specialist centers in carefully selected cases for diagnosis of some rare dementias (Level B).
References


Chapter 6 Brain Imaging in Evaluation of Dementia

Two categories of brain imaging can be used for diagnosis of dementia; structural imaging-computerized tomography (CT) and magnetic resonance imaging (MRI), and functional imaging- single photon emission computed tomography (SPECT) and positron emission tomography (PET). Traditionally, the role of brain imaging was emphasized solely in the context of ruling out a reversible cause of dementia. As its use has expanded, neuroimaging is now the most important ancillary investigation in the workup of dementia. Brain imaging aids in the differential diagnosis of Alzheimer disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), fronto-temporal dementia (FTD), Huntington’s disease, Creutzfeldt-Jacob disease (CJD), and normal pressure hydrocephalus (NPH), and in management decision.

A. Structural brain imaging

1. Types and functions of structural brain imaging

CT and MRI are the two most commonly utilized structural brain imaging modalities. CT is cost-effective and relatively quick, thus useful in patients with claustrophobia and patients who are contraindicated for MRI for reasons such as implanted cardiac pacemakers or metallic implants in brain. MRI is more costly than CT, but superior in detecting anatomical abnormalities and infarcts as well as white matter changes.

Structural brain imaging serves two purposes in patients suspected of dementia.

First, it is used to differentiate hemispheric lesions (brain tumor, subdural hematoma, hydrocephalus, etc.) that could cause cognitive impairment. Though varying among studies, the prevalence of reversible dementia is 1-10% out of all cases of dementia. The sensitivity and specificity of clinical consultation and neurological examinations to detect hemispheric lesions are approximately 90%. Without structural brain imaging, there is a risk of overlooking patients with potentially reversible causes of dementia. Farina et al performed CT in 513 patients with memory impairment, and a reversible cause of dementia was detected in 26 (7.2%) of them. Structural brain imaging is recommended in the early evaluation of patients with suspected dementia.

Second, structural imaging can be used to differentiate the cause of dementia. It is particularly useful in discriminating AD from VaD or FTD. In FTD, structural imaging reveals the hallmark finding of frontal lobe atrophy, but with a low sensitivity. VaD is associated with cerebrovascular disorders including cortical infarcts, lacunar lesions, and white matter changes, which are more easily diagnosed with MRI than CT.

Structural imaging is not used to provide an absolute diagnosis but to aid in clinical judgment about diagnosis and disease progress.

2. Computerized tomography

CT is mostly used to exclude other potentially treatable illnesses (for example, tumor, hematoma, and hydrocephalus). Measurement of medial temporal lobe width might help discriminate between depression and dementia, but can not between different causes of dementia.

3. Magnetic resonance imaging
MRI and CT have similar uses, but MRI has the ability to add increased specificity to the already high sensitivity of clinical diagnosis. MRI markers such as hippocampus volume might be useful in the early clinical diagnosis of AD and also be an adjunct in the differential diagnosis.

1) Significance and measurement of hippocampal atrophy in Alzheimer disease

Hippocampal atrophy is an early and specific marker of the AD process (de Leon et al, 1987; de Leon et al, 1989; DeCarli et al, 1995; Jack et al, 1992; Killiany et al, 1993). It has been measured using a variety of tracing techniques and anatomical boundaries. Some studies have employed linear or visual measurements (de Leon et al, 1996; Frisoni et al, 2002; O'Brien et al, 1997; Scheltens et al, 1997; Scheltens et al, 1995; Scheltens et al, 1992).

Several studies used a qualitative method that involves a visual rating scale, usually a four or five point scale ranging from absent to severe atrophy (Erkinjuntti et al, 1993). Visual assessment is considerably less time-consuming than volumetry and easily applicable in the clinical setting (Wahlund et al, 1999). The down-side may be a larger inter-rater variability (Scheltens et al, 1995). Pucci et al argued that the most discriminating parameter is the height of the left hippocampus (Pucci et al, 1998). Reports of sensitivity and reliability vary depending on methodology and anatomical locations of measurement. Frisoni et al used a compound score of linear measurements that included the temporal horn of ventricle. In this novel approach, Frisoni and co-workers used the radial width of the temporal horn of the lateral ventricle on axial MR scans as measured with a calliper on paper printouts (Frisoni et al, 2002). Though debatable, other studies have used volumetric measures of medial lobe temporal structures for supposedly better accuracy and reliability. Comparative studies have found good correlation between these assessment techniques (Desmond et al, 1994; Wahlund et al, 2000).

2) Magnetic resonance imaging in vascular dementia

In the most commonly used National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) international work group criteria for VaD, neuroimaging is essential for diagnosis, and without it, VaD is deemed ‘possible’ at best (Roman et al, 1993). Furthermore, the criteria specify which vascular territories are relevant for VaD. These include large vessel strokes, such as bilateral infarcts in the anterior or posterior cerebral artery areas, association areas, or watershed regions. Using operational guidelines on how to classify radiological features as fitting into the NINDS-AIREN criteria, inter-observer reliability of the diagnosis significantly improved from 40% to 60% (van Straaten et al, 2003) (II).

Like AD, the prevalence and morbidity of cerebrovascular disease (CVD), both symptomatic and asymptomatic, increases with age in VaD. In addition, concomitant cerebral infarction might be found in patients with definite AD (Snowdon et al, 1997). Even small, concurrent infarctions significantly increase the likelihood of expressed dementia, suggesting a synergistic effect. Given that concurrent CVD might be amenable to treatment interventions aimed at ameliorating the disease progression, brain imaging may prove important to the clinical care of the demented patient with coexisting CVD. Preliminary
evidence from anti-hypertensive treatment trials of older individuals supports this notion, though further clinical trials on brain imaging are necessary.

3) Magnetic resonance imaging in other dementias

In DLB, MRI has been reported to show medial temporal lobe atrophy in a lower frequency than in AD. Therefore, the absence of medial temporal lobe atrophy may be suggestive of a diagnosis of DLB (Barber et al, 1999).

In FTD, asymmetric, predominantly left-sided peri-sylvian atrophy characterizes progressive non-fluent aphasia. Asymmetric anterior temporal lobe atrophy is diagnostic of semantic dementia (SD). In both conditions, atrophy becomes more widespread with time, but usually remains asymmetric. The pattern of atrophy might be more useful than atrophy of single regions in the differential diagnosis of FTD versus AD.

In Huntington’s disease, bilateral caudate atrophy is observed on MRI. In CJD, hyperintense signal in the basal ganglia is observed in sporadic CJD, while hyperintense signal change in the thalamic pulvinar is observed in new variant CJD (Schroter et al, 2000). Diffusion-weighted MRI shows focal changes in CJD that are not apparent on FLAIR images, and may widely involve the cortex.

In NPH, strict adherence to clinical and MRI criteria is important. Clinical diagnosis is often difficult, and it may not be easy to decide whether such a patient would benefit from a shunting procedure. The predictors of a positive shunt response include improvement in clinical symptoms such as gait disturbance after CSF drainage and the occurrence of B-waves (0.5-2/minute oscillation) for at least 50% of the recording time on continuous CSF monitoring (Vanneste, 2000). MRI criteria include widened ventricles with normal sulci and without white matter pathology.

Corticobasal degeneration shows a typical MRI pattern, with striking asymmetric parietal and frontal atrophy, with sparing of the medial temporal regions (Kitagaki et al, 2000).

B. Functional brain imaging in dementia

1. Types and functions of functional brain imaging

The most often performed functional brain imaging techniques in the evaluation of dementia includes technetium-99m hexamethylpropyleneamine oxime (99mTc-HMPAO) SPECT and [18F]fluoro-2-deoxy-D-glucose (FDG) PET. SPECT measures regional blood flow while FDG PET measures glucose metabolism. Reduction in blood flow or glucose metabolism in parieto-temporal areas is the most common finding on functional brain imaging of AD. However a study reported that MRI was more useful in diagnosis of dementia than PET or SPECT. Though none of these tests are as effective as neuropsychological examinations. Delayed recall assessment is at least as effective as MRI-based brain volumetry in distinguishing between probable AD and normal controls. Though functional brain imaging is not as effective as MRI or neuropsychological examinations in diagnosis of dementia, it shows higher specificity than the clinical diagnosis in differentiation among other subtypes of dementia. Therefore, use of functional brain imaging such as SPECT and PET might aid in differential diagnosis when used
together with structural brain imaging in patients suspected of dementia. Other functional brain imaging such as functional MRI, MR spectroscopy, diffusion-weighted MR, Magnetoencephalogram (MEG), and amyloid PET imaging have been reported to distinguish AD from other dementias. Their clinical use, however, is not recommended due to the high cost, limited efficacy, and the lack of supporting evidence.

2. Single photon emission computed tomography

A systematic review and several follow-up studies have demonstrated the usefulness of SPECT in diagnosis of AD. While clinical diagnostic criteria show a higher sensitivity than SPECT, SPECT shows a higher specificity in differentiating subtypes of dementia in comparison. SPECT is useful in distinguishing AD from VaD, DLB, or FTD.

Perfusion HMPAO SPECT is used to discriminate among AD, VaD, and FTD when diagnostic certainty is low. SPECT is not very useful in patients with Down syndrome since they might present SPECT abnormalities similar to AD throughout the life cycle. Where HMPAO SPECT can not be used, FDG PET aids in differentiation of AD, VaD, and FTD with diagnostic uncertainty. Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT is used to aid in diagnosis when DLB is suspected. HMPAO SPECT and FDG PET provide highly valuable information in evaluation and diagnosis of patients suspected of dementia.

Clinical criteria (pathologically verified) were shown more sensitive in detecting AD than brain SPECT (81% versus 74%). However, SPECT showed a higher specificity against other types of dementia than the clinical criteria (91% versus 70%). Therefore, SPECT may be helpful in cases of FTD or VaD that need to be differentiated from AD. FP-CIT SPECT might provide useful information when DLB is suspected. Based on Class II studies, the sensitivity of SPECT for the diagnosis of dementia was lower than that of the clinical diagnosis (Mattman et al, 1997; Van Gool et al, 1995). In a single prospective study, when specificity was set at 89%, overall sensitivity was 43% (Van Gool et al, 1995).

3. [18F]fluoro-2-deoxy-D-glucose positron emission tomography

FDG PET is slightly superior to perfusion SPECT in detecting dementia (Mielke and Heiss, 1998). The largest series of dementia cases who underwent PET scans and autopsy confirmation was reported in a Class II study that included 22 patients with various types of dementia (64% AD) (Hoffman et al, 2000). In this study, visual interpretations of PET scans, which have high inter-rater reliability (Hoffman et al, 1996), yielded a sensitivity of 93% and a specificity of 63%. The FDG-PET findings in AD are summarized below. First, pathological changes in AD are not globally observed across the brain at the same time. In the early stage of AD, parieto-temporal hypometabolism is prominent, and symptoms such as memory impairment, disorientation, and difficulties with naming, calculation, writing, and reading appear earlier. Personality changes develop later as AD progresses and frontal lobe hypometabolism becomes marked. Second, there is a qualitative difference between AD and normal aging. The pattern of parieto-temporal hypometabolism seen in AD is not observed in normal older adults. Rather, frontal hypometabolism shown in an advanced AD appears earlier in normal aging (Shaw et al, 1984; Gur et al, 1987; Mielke et al,
Third, there is a difference in metabolic findings between presenile AD and senile AD. Hypometabolism was more global in senile AD whereas the metabolic impairment was more localized in presenile AD (Mielke et al, 1992). Fourth, symptoms in dementia are also subject to localization or lateralization as seen in stroke or brain tumor. Fifth, pathological changes in AD invade not only cortical but subcortical structures. Sixth, there is correlation between the severity of dementia and the extent of hypometabolism (Foster et al, 1984).

C. Molecular imaging of the brain in dementia

1. Amyloid positron emission tomography

In the late 1990s, a new PET imaging technique that could detect β amyloid deposition in the living human brains was developed, providing fundamental insight into the progression of AD (Agdeppa et al, 2001). The hypothesis theorizes that the neuronal degenerative changes observed in patients with AD are caused by the production, aggregation, and deposition of β amyloid formed by dysmetabolism of amyloid precursor proteins. Fluorescent labeled monoclonal antibodies to β amyloid or isotope-tagged probes that selectively bind to β amyloid are injected into patients with AD to be imaged by PET or SPECT. These methods allow direct visualization of the amyloid plaques accumulated in the brain tissue, and related results in animal and several clinical studies have been reported (Friedland et al, 1997; Shogi-Jadid et al, 2002; Klunk et al, 2004). Apart from amyloid plaques, neurofibrillary tangles were visualized in another study (Shogi-Jadid et al, 2002). Of several amyloid-binding imaging probes, Pittsburgh Compound-B (PIB) has been the most expensively studied.
1. Structural imaging should be used in the evaluation of every patient suspected of dementia (Level A).

2. CT can be used to identify surgically treatable lesions and vascular disease (Level A).

3. MRI (with a protocol including T1, T2 and FLAIR sequences) should be used to increase specificity for diagnosis of dementia (Level A).

4. Of functional imaging, SPECT and PET may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up. They should not be used as the only imaging measure (Level B).
References


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