Chapter 2

Syndrome, Rating Scales, Tests, Diagnosis

Objective

To understand the symptoms and rating scales of dementia, to conduct the necessary tests, and to diagnose dementia accurately.

Symptoms

The dementia syndrome comprises impairment of cognitive functions including memory, language, and visuospatial cognition, together with associated behavioral and psychological symptoms of dementia (BPSD). Multiple cognitive functions are impaired, reflecting the sites of functional decline in various disorders. The basis of BPSD is cognitive impairment, and arise as a result of influences by physical factors, environmental factors, and psychological factors. Various rating scales have been devised to prevent overlooking symptoms and to monitor changes over time.

History taking

Taking history from the patient, family members, and caregivers is important. By taking history from the patient, cognitive functions such as memory, language, and thinking; the degree of disease awareness; and psychological symptoms can be estimated. Ask family members about specific symptoms and their changes over time. Ask about the patient's life history including handedness, educational history, and occupation, which will be useful to estimate the patient's capabilities before disease onset and to explore the mechanisms of BPSD.

CQ 2-1

What kinds of cognitive function impairment are found in dementia?

Answer

Multiple cognitive functions are impaired in dementia, reflecting the sites of functional decline in various disorders. The main cognitive function impairments include general attention impairment, amnesia, aphasia, visuospatial impairment, apraxia, and executive function impairment.

Comments and evidence

As a part of the neurological examination, neuropsychological evaluations for the cognitive functions shown below can be used to capture the characteristic cognitive impairment of each disease [1].

1. General attention impairment

General attention is a function that forms the basis of perceiving and selecting stimulation in the surrounding and acting appropriately in response to the stimulation. In dementia, the retention, selectivity, and allocation of attention are often impaired from a relatively early stage, regardless of the etiological subtype, subsequently affecting various individual cognitive functions. If general attention is impaired, the amount of information that can be processed at one time is reduced, making it difficult to understand, memorize, and react to relatively complex matters.

2. Executive function impairment

Executive function refers to the functions of planning and executing a task with a purpose, and carrying on with the task while continuously feeding back the result. Impairment of executive function is a typical symptom of frontotemporal lobar degeneration (FTLD), but may also be present in other types of dementia. Executive function is related to all the complex actions, and its impairment may become noticeable when work and housework are not carried out in a usual manner.

3. Memory impairment

Memory is a function by which new experience is preserved, and that experience is reproduced in consciousness or action [2]. Memory includes the process of memorizing the experience, retaining (storing) it for a certain period, and then retrieving (recalling) the experience. Memory is classified according to the contents to be memorized and the period of retention as follows.

a. Classification by content

Declarative memory refers to the memory that can be consciously recalled and expressed verbally. Non-declarative memory is the memory that cannot be expressed explicitly; an example is procedural memory. Declarative memory is subdivided into episodic memory and semantic memory.

Episodic memory is the memory of events including the context of when and where, and impairment of episodic memory is called amnesia. Amnesia is observed in many types of dementia, and is a particularly common manifestation in the early stage of Alzheimer's disease. Episodic memory deficit is further divided into retrograde amnesia which is failure to recall events before the onset of disease, and anterograde amnesia which is failure to recall events after the onset of disease.

Semantic memory is equivalent to knowledge including meaning of objects and names. In semantic dementia, the patient initially cannot recall the names of objects, gradually cannot understand when being told the names of objects, and eventually cannot understand even though when being shown the actual objects.

Non-declarative memory includes procedural memory of skills such as riding a bicycle. Since non-declarative memory is preserved even in an amnestic patient, it may be useful for maintaining activities of daily living.

b. Classification by length of retention

Based on the length of time a stimulus is retained, memory can be divided into immediate (short-term) memory, recent memory, and remote memory. Immediate memory is a function related to general attention, while recent and remote memory are episodic memory. Immediate memory is a function that stores a stimulus for a few seconds and reproduces it immediately,

and can be tested, for example, by forward digit span. To assess the presence or absence of amnesia, it is necessary to test the episodic memory by asking the patient to memorize a stimulus and then to recall after other tasks have been completed.

c. Other types of memory

Working memory is a function that uses immediate memory to hold information and utilizes it to perform cognitive task. The task of sequentially subtracting 7 from 100 corresponds to this memory. Prospective memory is the function of remembering a planned action and executing it at an appropriate time and situation.

4. Aphasia

Aphasia refers to the state of impairment at the language level while basic functions such as articulation and hearing are preserved. Primary progressive aphasia is a subtype in which aphasia presents as the first symptom, and remains a foreground symptom as dementia advances (see CQ2-6). Aphasia coexists commonly with dementia.

5. Visuospatial impairment

Visuospatial impairment is commonly found in Alzheimer's disease and dementia with Lewy bodies (DLB), which are mainly related to posterior cerebral functions. Constructional apraxia can be detected by the inability to copy drawings and imitate hand postures. In dementia with Lewy bodies, illusion and vivid visual hallucination are found. Posterior cortical atrophy (PCA) is an atypical dementia with visuospatial impairment as the dominant symptom, and is commonly caused by Alzheimer's disease.

6. Apraxia

Apraxia refers to the failure to perform habitual movements or using tools, which cannot be explained by impaired motor ability or object recognition. Limb-kinetic apraxia mainly refers to a state of clumsy upper limb movement, and may be seen in corticobasal degeneration. Ideomotor apraxia (inability of gestures and habitual movements), ideational apraxia (inability of using tools), and dressing apraxia (inability of getting dressed) may occur in various subtypes of dementia. However, apraxia is often complicated by visuospatial impairment and extrapyramidal symptoms, manifesting complicated clinical presentations.

7. Social cognition impairment

Impairment of social cognition is the failure to recognize emotions and situations, and to act accordingly.

■ References

1) Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol. 2014; 10(11): 634-642.
2) Yamadori A. Neuropsychology of Memory. Tokyo: Igaku Shoin; 2002. (In Japanese)

CQ 2-2

What are the behavioral and psychological symptoms of dementia (BPSD)?

Answer

The basis of BPSD is cognitive impairment of dementia, and BPSD arise as a result of influences by physical factors, environmental factors, and psychological factors [1,2]. They consist of behavioral symptoms such as agitation, aggression, and disinhibition, and psychological symptoms including anxiety, depression, hallucination, and delusion.

Comments and evidence

Based on the classification of BPSD in Alzheimer's disease reported by the European Alzheimer Disease Consortium [1, 2], this section outlines the BPSD of Alzheimer's disease and other subtypes of dementia.

1. Symptoms related to hyperactivity

These symptoms include agitation, irritability, disinhibition, and abnormal behaviors. When patients become aware of their forgetfulness and start feeling anxious and frustrated, they get upset by even trivial matters leading to irritability. And, when fueled by inappropriate responses from people around them, they may develop into aggression and agitation such as using abusive language and violence. Behavioral symptoms include wandering and aggressive behaviors, which are related to various underlying cognitive impairments, and necessitate individual management.

2. Psychosis-like symptoms

These symptoms include hallucination, delusion, and nocturnal abnormal behaviors. Delusion is a false belief that cannot be corrected, and is caused by psychological factors with amnesia and misperception in the background. Delusion of theft and persecutory delusion are well known in Alzheimer's disease, while jealousy delusion and phantom boarder delusion are well known in DLB. Visual hallucination and REM sleep behavior disorder are considered to be one of the core symptoms of DLB.

3. Symptoms related to affective symptoms

Anxiety and a depressive state are often observed in the early stage of Alzheimer's disease. For DLB, more than one half of the patients show a depressive state during the course of disease, and these symptoms are included as supportive features in the diagnostic criteria of DLB. In addition, a depressive state is the first symptom of DLB in a considerable number of patients.

4. Symptoms related to apathy

Apathy refers to reduced spontaneity and motivation. Apathetic symptoms may manifest in the affective domain such as lack of emotions, in the behavioral domain such as inactivity, and in the cognitive domain such as lack of interest toward the surrounding. Unlike depression, apathy is characterized by a lack of feeling of sorrow and self-accusation. Apathy is seen at a high frequency in frontotemporal lobar degeneration, while it is the most common BPSD symptom in Alzheimer's disease, and is also found in more than one-half the patients with DLB.

■ References

1) Aalten P, Verthey FRJ, Boziki M, et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: Part I. Dement Geriatr Cogn Disord. 2007; 24(6): 457-463.
2) Aalten P, Verthey FRJ, Boziki M, et al. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. Dement Geriatr Cogn Disord. 2008; 25(1): 1-8.

CQ 2-3

What are the useful scales for assessing cognitive impairment in dementia?

Answer

As a useful scale for evaluating cognitive impairment in dementia, the Mini Mental State Examination (MMSE) is widely used internationally in clinical setting and in research. It is desirable to add necessary tests according to the subject evaluated, the purpose and the environment, and interpret the results taking into account the background and condition of each patient. C

Comments and evidence

MMSE is widely used internationally in the clinical setting and in research as a screening for cognitive impairment. The maximum MMSE score is 30 points; 29 points for tests including language function and 1 point for copying a drawing. In general, a score of 23 points or below indicates a suspicion of dementia. The sensitivity is low in mild patients, in patients with high premorbid ability, and in patients with visuospatial impairment as the main symptom [1]. Even in mild dementia, the score will be low when the patient has language impairment. In Japan, the Revised Hasegawa's Dementia Scale (HDS-R) is also commonly used and has a high correlation with MMSE. There are no tasks that can be performed nonverbally in HDS-R. In general, a score of 20 or below indicates a suspicion of dementia.

For mild dementia and mild cognitive impairment (MCI), the Montreal Cognitive Assessment-Japanese version (MoCA-J) and the Japanese version of Addenbrooke's Cognitive Examination-Revised (ACE-R) are used (See CQ4B-4). Moreover, adding neuropsychological tests such as trail making test and logical memory task to MMSE increases the rate of diagnosing mild dementia [2]. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (Japanese version) (ADAS-Jcog) is an examination centered on memory and visuospatial recognition, and is used to evaluate the changes of Alzheimer's disease symptoms.

If more detailed examinations are required to assess various cognitive functions, select the appropriate tests. Severe Impairment Battery (SIB) [3, 4] and Severe Cognitive Impairment Rating Scale (SCIRS) [5, 6] are assessments for patients with severe dementia.

It is essential to evaluate cognitive dysfunction not only based on the cutoff values of various tests alone, but also to consider the patient's premorbid ability as well as the physical and mental states at the time of testing. Estimating the cognitive and behavioral changes from premorbid state is important.

References

1) Velayudhan L, Ryu SH, Raczek M, et al. Review of brief cognitive tests for patients with suspected dementia. Int Psychogeriatric. 2014; 26(8): 1247-1262.
2) Wouters H, Appels B, van der Flier WM, et al. Improving the accuracy and precision of cognitive testing in mild dementia. J Int Neuropsychol Soc. 2012; 18(2): 314-322.
3) Saxton J, McGonigle-Gibson KL, Swihart A, et al. Assessment of the severely impaired patient: description and validation of a new neuropsychological test battery. Psychol Assess. 1990; 2(3): 298-303.
4) Niina R, Honnma A, Sugai Y. Reliability, validity and clinical usefulness of the Japanese version of SIB and Japanese version of revised ADCS-ADL. Japanese Journal of Geriatric Psychiatry. (Ronen Seishin Igakushi) 2005; 16(6): 683-691. (In Japanese)
5) Choe JY, Youn JC, Park JH, et al. The Severe Cognitive Impairment Rating Scale-an instrument for the assessment of cognition in moderate to severe dementia patients. Dement Geriatr Cogn Disord. 2008; 25(4): 321-328.
6) Tanaka H, Uematsu M, Nagata Y, et al. Cognitive function test for severe dementia patients: Clinical usefulness of the Japanese version of Severe Cognitive Impairment Rating Scale. Japanese Journal of Geriatric Psychiatry. (Ronen Seishin Igakushi) 2013; 24(10): 1037-1046. (In Japanese)

Search formula

PubMed search: July 15, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis OR diagnoses OR diagnostic)) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND (diagnosis OR diagnoses OR diagnostic))) AND ("Neuropsychological Tests" [Majr] OR neuropsychological test* [TI] OR "Psychiatric Status Rating Scales" [Majr] OR assessment scale* [TI])

Ichushi search: July 15, 2015 (Wednesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function/TI) AND (Neuropsychological examination/TH OR Neuropsychological examination/TI OR Neuropsychological tests/TI OR Psychiatric rating scale /TH OR rating scale/TI)

CQ 2-4

What are the useful rating scales for behavioral and psychological symptoms of dementia (BPSD), activities of daily living (ADL), and global severity?

Answer

The Neuropsychiatric Inventory (NPI) is a rating scale for BPSD, and Physical Self-Maintenance Scale (PSMS) is a rating scale for ADL . The Clinical Dementia Rating (CDR) is widely used to evaluate global severity, and the Japanese version is available. C

Comments and evidence

BPSD, ADL, and global severity are evaluated based on the behaviors of a person with dementia in various situations as observed by other persons. Since the methods of observing behavior may be affected by the observer's skill and condition, an appropriate rating method should be selected considering the patient's environment including the caregivers.

1. Evaluation of BPSD

BPSD are evaluated based on a semi-structured interview with the caregiver who closely observes the behaviors of the person with dementia. The NPI evaluates the presence or absence, frequency, and severity of 10 domains of psychiatric symptoms (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, dysphoria, apathy, disinhibition, irritability, and aberrant motor behavior). Recently, a 12-domain version with the addition of two domains; nighttime behavior disturbance and appetite/eating abnormalities, is commonly used. This tool is widely used internationally and is also commercially available in Japan. A questionnaire version (NPI-Q) and a nursing home version (NPI-NH) are available. The Behavioral Pathology in Alzheimer 's Disease (Behave-AD) has 25 items and is scored on a 4-point severity scale. The Cohen-Mansfield Agitation Inventory (CMAI) is a scale that systematically evaluates the frequency of 29 agitated behaviors rated on a 7-point scale.

2. Evaluation of ADL

Patients with dementia have disability in daily living, and the core disability is deterioration of ADL. The Physical Self-Maintenance Scale (PSMS) consists of 6 basic ADL items (toilet, feeding, dressing, grooming, physical ambulation, and bathing), and Instrumental ADL Scale (IADL) consists of 8 ADL items using instruments (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility of own medications, and ability to handle finance), both of which are rated by the caregiver. These scales are widely used internationally, and Japanese versions of both scales are also available [1].

3. Evaluation of global severity

The Clinical Dementia Rating (CDR) is widely used internationally. It is an evaluation method based on a semistructured interview with the patient's caregiver regarding six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care. The patient's impairment of each item is scored, and the global score is classified into five stages: 0; normal, 0.5: very mild dementia, 1: mild dementia, 2: moderate dementia, 3: severe dementia. Attention is required when there is insufficient information from the caregiver or when the rater's training is insufficient, because inter-rater agreement may not be adequate. Based on CDR, a method that considers a simple cognitive function test for the patient, a method that uses the total score of the 6 items, and a revised shortened version have been proposed [2]. Rating scales that were developed in Japan, including the Nishimura Mental Scale as well as the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) that examines changes between two time points [3], are also used.

■ References

1) Sikkes SA, de Lange-de Klerk ES, Pijnenburg YA, et al. A systematic review of instrumental activities of daily living scales in dementia: room for improvement. J Neurol Neurosurg Psychiatry. 2009; 80(1): 7-12.

2) Duara R, Loewenstein DA, Greig-Custo MT, et al. Diagnosis and staging of mild cognitive impairment, using a modification of the clinical

dementia rating scale: the mCDR. Int J Geriatr Psychiatry. 2010; 25(3): 282-289.
3) Nakamura Y, Usui M, Nishikawa T, et al. CIBIC Plus-J assessment using a videotaped method in Alzheimer's disease patients. Dement Geriatr Cogn Dis Extra. 2012; 2(1): 271-277.

■ Search formula

PubMed search: July 15, 2015 (Wednesday)
#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis OR diagnoses OR diagnostic)) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND (diagnosis OR diagnoses OR diagnostic))) AND ("Neuropsychological Tests" [Majr] OR neuropsychological test* [TI] OR "Psychiatric Status Rating Scales" [Majr] OR assessment scale*[TI])

Ichushi search: July 15, 2015 (Wednesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function/TI) AND (Neuropsychological examination/TH OR Neuropsychological examination/TI OR Neuropsychological test/TI OR Neuropsychological rating scale/TH OR Rating scale/TI)

CQ 2-5

How is quality of life (QOL) evaluated in persons with dementia?

Answer

There are various viewpoints regarding the methods of QOL evaluation in people with dementia. Although there is no standard method, an appropriate one can be selected and used through considering the severity and environment of the person with dementia. C

Comment and evidence

QOL is a concept that integrates physical and mental functions, ability of performing activities of daily living, and social activities. The evaluation method varies depending on how the concept is perceived. QOL evaluation methods are broadly divided into self-rating and rating by others (proxy-rating), and a combination of the two. Self-rating becomes more difficult as dementia progresses, and proxy rating has limitations including observer bias [1].

SF-36 and EQ-5D are widely used internationally as self-rating methods for overall health-related QOL, but they are difficult to score for persons with advanced dementia and therefore have low validity in persons with dementia [2]. In English-speaking countries, there are more than 15 QOL rating methods specialized for dementia [3], but the definition and focus of QOL differ depending on the rating method, and there is no standard.

Quality of Life in Alzheimer's Disease (QoL-AD) [4], a simple rating method that combines self-rating and caregiver-rating, is suitable for Alzheimer's disease dementia up to moderate severity, and is widely used in clinical research [5].

References

1) Graske J, Meyer S, Wolf-Ostermann K. Quality of life ratings in dementia care-across-sectional study to identify factors associated with proxy-ratings. Health Qual Life Outcomes. 2014; 12: 177.
2) Smith S, Lamping D, Banerjee S, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. Health Technol Assess. 2005; 9(10): 1-93.
3) Perales J, Cosco TD, Stephan BC, et al. Health-related quality of life in the Cambridge City over-75s Cohort (CC75C): development of a dementia-specific scale and descriptive analyses. BMC Geriatr. 2014; 14: 18.
4) Logston RG, Gibbons LE, McCurry SM, et al. Quality of life in Alzheimer's disease: patient and caregiver reports. J Ment Health Aging. 1999; 5(1): 21-32.
5) Matsui T, Nakaaki S, Murata Y, et al. Determinants of the quality of life in Alzheimer's disease patients as assessed by the Japanese version of the Quality of Life-Alzheimer's disease scale. Dement Geriatr Cogn Disord. 2006; 21(3): 182-191.

Search formula

PubMed search: July 15, 2015 (Wednesday)

#1 ("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR cognition disorder* [TI] OR cognitive disorder* [TI]) AND ("Neuropsychological Tests" [Majr] OR neuropsychological test* [TI] OR "Psychiatric Status Rating Scales" [Majr] OR scale* [TI]) AND ("Quality of Life" [Majr] OR "quality of life" [TI])

Ichushi search: July 15, 2015 (Wednesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function/TI) AND (Neuropsychological examination/TH OR Neuropsychological examination/TI OR Neuropsychological test/TI OR Neuropsychological rating scale/TH OR Rating scale/TI) AND (QOL/TH OR QOL/TI OR "Quality of Life"/TI)

CQ 2-6

How is primary progressive aphasia (PPA) classified and evaluated?

Answer

Primary progressive aphasia (PPA) can be divided into (1) non-fluent/agrammatic type, (2) semantic type, and (3) logopenic type. Clinical classification is based on assessment of language and semantic memory as well as lesion distribution. C

Comments and evidence

PPA refers to a group of degenerative dementia that manifests aphasia as the onset symptom, and aphasia remains the foreground symptom as disease progresses. PPA is divided into 3 types according to the characteristics of aphasia. The 3 types show characteristic distribution of site of atrophy on MRI and site of decreased blood flow/metabolism on SPECT/PET [1].

For clinical diagnosis, examine the patient for speech production features (motor speech, sound errors, and word-finding pauses), single-word and syntax comprehension, functions of confrontation naming and repetition, and reading/writing. The non-fluent/agrammatic type is characterized by inconsistent speech sound errors called apraxia of speech as well as agrammatism in speech/comprehension, but some patients manifest only one of these features. A variant of this type is primary progressive apraxia of speech manifesting only apraxia of speech without aphasia, which has similar site of atrophy as non-fluent/agrammatic type PPA with prominent apraxia of speech [2]. In the semantic type, impaired single-word comprehension and confrontation naming are the core symptoms, which progress to impairment of semantic memory such as object knowledge. Speech fluency and repetition are spared. As disease progresses, semantic memory is impaired, and the patient becomes unable to understand even when being shown an object. The logopenic type manifests impaired single-word retrieval in spontaneous speech and naming. While single word comprehension and repetition are spared, repetition of sentences and phrases is impaired and phonetic errors are prominent.

The Western Aphasia Battery (WAB) and Standard Language Test of Aphasia (SLTA) are used for semi-quantitative evaluation of language. However, it has been reported that using a picture description task can reveal the distinct speech characteristics [3]. Using the current diagnostic criteria, approximately one-third of the cases cannot be classified into any of the clinical types, while some cases are classified into two types. Reconsidering the classification may be required [4].

Since PPA is a clinical syndrome, it has heterogeneous neuropathologic causes. Regarding agreement of PPA classification with pathological diagnosis, 77% of patients with non-fluent/agrammatic variant PPA had frontotemporal lobar degeneration (FTLD) (tau; 51%, TDP-43; 26%), and 21% of them had Alzheimer's disease. Moreover, 88% of the patients with semantic variant PPA had FTLD (tau; 15%, TDP-43; 73%), and 12% of them had Alzheimer's disease. Finally, 56% of the patients with logopenic variant PPA had Alzheimer's disease and 36% of them had FTLD (tau; 11%, TDP-43; 24%) [5, 6]. Roughly speaking, the semantic variant is strongly related to FTLD-TDP, while about a half of the non-fluent/agrammatic variant is related to FTLD-tau and about a half of the logopenic variant is related to Alzheimer's disease.

References

1) Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; 76(11): 1006-1014.
2) Josephs KA, Du-y JR, Strand EA, et al. Syndromes dominated by apraxia of speech show distinct characteristics from agrammatic PPA. Neurology. 2013; 81(4): 337-345.
3) Ash S, Evans E, O'Shea J, et al. Differentiating primary progressive aphasias in a brief sample of connected speech. Neurology. 2013; 81(4): 329-336.
4) Botha H, Du-y JR, Whitwell JL, et al. Classification and clinicoradiologic features of primary progressive aphasia (PPA) and apraxia of speech. Cortex. 2015; 69: 220-236.
5) Harris JM, Gall C, Thompson JC, et al. Classification and pathology in primary progressive aphasia. Neurology. 2013; 81(21): 1832-1839.
6) Harris JM, Jones M. Pathology in primary progressive aphasia syndromes. Curr Neurol Neurosci Rep. 2014; 14(8): 466.

Search formula

PubMed search: July 15, 2015 (Wednesday)

#1 ("Aphasia, Primary Progressive/classification" [Majr] OR ("primary progressive aphasia" [TI] AND classification) OR (("Aphasia, Primary Progressive/diagnosis" [Mesh] OR ("primary progressive aphasia" [TI] AND (diagnosis OR diagnoses OR diagnostic))) AND ("Neuropsychological Tests" [Mesh] OR neuropsychological test* [TI]) AND assessment*)) OR (("Aphasia, Primary Progressive/diagnosis" [Majr] OR ("primary progressive aphasia" [TI] AND (diagnosis OR diagnoses OR diagnostic)) OR (("Aphasia, Primary Progressive/diagnosis" [Mesh] OR ("primary progressive aphasia" [TI] AND (diagnosis OR diagnoses OR diagnostic))) AND ("Neuropsychological Tests" [Mesh] OR neuropsychological test* [TI]))) AND (three variant* OR (variant* AND (criteria [TI]OR "Diagnosis, Differential" [Mesh] OR "differential diagnosis" [TI] OR classification [TI] OR classification [SH] OR assessment* [TI])))

Ichushi search: July 15, 2015 (Wednesday)

#1 (Aphasia-primary progressive/TH OR Primary progressive aphasia/TI) AND (Classification/TH OR Classification/AL OR Evaluation/AL OR Criteria/AL OR Variation/TH OR Variation/AL OR Variant/AL)

CQ 2-7

How is dementia diagnosed and differentiated?

Answer

For clinical diagnosis of dementia, history taking as well as physical and neurological examinations are important. During this step, efforts should be made to comprehensively understand whether dementia is present, and if so, the symptoms and severity of dementia. Then conduct cognitive function tests, structural brain imaging (CT or MRI), functional brain imaging, as well as blood and cerebrospinal fluid tests to diagnose the type of dementia. In this process, efforts should be made not to overlook treatable dementia, and to rule out delirium, depression, and drug-induced cognitive impairment.

Comments and evidence

Dementia can be summarized as "a state of continuous impairment of multiple acquired cognitive and mental functions, not due to disturbance of consciousness, to the extent that daily living and social life are affected". Diagnosis of dementia requires two steps. First, determine whether the patient has dementia by comprehensively confirm whether the functions of daily living are disabled due to acquired and chronic cognitive impairment [1]. In this process, perform history taking and cognitive function tests. Definitions of and diagnostic criteria for dementia are provided by the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) [2], the Diagnosis and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) [3], and the criteria of the National Institute on Aging–Alzheimer's Association workgroup (NIA-AA) [4]. Even when the conditions of a case do not meet the criteria for dementia, it may be classified into the category of mild cognitive impairment if there is cognitive impairment present in the background.

The next step is to determine the underlying disease of dementia. In this process, perform various examinations as necessary, such as physical findings, neurological examinations, imaging examinations, and blood and cerebrospinal fluid tests. In order not to overlook treatable dementia, it is desirable to perform structural imaging by head CT or MRI when dementia is diagnosed [5-7]. Blood counts, hematology and blood biochemistry, as well as measurements of thyroid hormone, electrolytes, fasting blood glucose, vitamin B_{12}, and folic acid are recommended. Cerebrospinal fluid test is recommended for patients with atypical types and other conditions that are difficult to differentiate [5-7]. In view of the diverse differential diagnoses for juvenile dementia, consider referring the patient to a specialist [1].

Refer to the dementia diagnosis flowchart (2017) modified from the previous version published in Treatment Guideline for Dementia 2010.

References

1) Galvin JE, Sadowsky CH. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med. 2012; 25(3): 367-382.
2) World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Geneva: World Health Organization; 1993.
3) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Arlington, VA: American Psychiatric Association; 2013.
4) McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-269.
5) Noel-Storr AH, McCleery JM, Richard E, et al. Reporting standards for studies of diagnostic test accuracy in dementia: The STARDdem Initiative. Neurology. 2014; 83(4): 364-373.
6) Sorbi S, Hort J, Erkinjuntti T, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol. 2012; 19(9): 1159-1179.
7) Arai H. Diagnosis of dementia. Japan Society of Dementia Research (Ed.) Textbook of Dementia. Tokyo: Chugai Igakusha; 2008: 158-163. (In Japanese)

Search formula

PubMed search: July 1, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis[TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Diagnosis, Differential" [Majr] OR "differential diagnosis" [TI] OR "Diagnostic Errors" [Majr] OR diagnostic error* [TI] OR misdiagnosis [TI])

Ichushi search: July 1, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Differential diagnosis/MTH or Differentiation/TI or Misdiagnosis/MTH or Misdiagnosis/TI)

CQ 2-8

How are imaging examinations carried out in dementia?

Structural imaging (CT or MRI) is used to exclude treatable dementia. On MRI, the brain atrophy pattern in brain regions, and the presence and distribution of signal changes are useful for differential diagnosis of dementia. Functional imaging techniques such as cerebral blood flow single-photon emission computerized tomography (SPECT), dopamine transporter scintigraphy, and MIBG myocardial scintigraphy are also useful for differential diagnosis of dementia.

B

Comment and evidence

It is desirable to perform structural imaging test (CT or MRI) to exclude dementia treatable by neurosurgery, such as chronic subdural hematoma, brain tumor, and normal pressure hydrocephalus [1]. In addition, MRI is superior for discriminating brain atrophy patterns, which is useful for differential diagnosis [2]. Evaluation of signal changes on MRI is useful for differential diagnosis of cerebrovascular diseases, leukoencephalopathy, encephalitis, demyelinating diseases, and others [2].

The basic MRI sequences are T1-weighted image, T2-weighted image, and FLAIR image. When a brain tumor, inflammatory lesion, or infectious lesion is suspected, perform contrast enhanced imaging to look for contrast enhancement [3]. Diffusion-weighted images are superior for detecting acute cerebral vascular lesions and lesions with high signal intensity in the cerebral cortex or striatum/thalamus in Creutzfeldt-Jakob disease. T2*-weighted imaging and susceptibility-weighted imaging (SWI) are excellent for detecting micro-hemorrhages in amyloid angiopathy.

Cerebral blood flow SPECT is useful for differential diagnosis of dementia due to lesions with low blood flow. Cerebral blood flow SPECT uses nuclides such as ^{123}I-IMP and ^{99m}Tc-ECD. Cerebral blood flow SPECT images can be interpreted visually or analyzed using statistical methods [such as 3D-stereotactic surface projection (3D-SSP) and easy Z-score imaging system (eZIS)]. Alzheimer's disease dementia is characterized by decreased blood flow in the posterior cingulate gyrus, anterior wedge, and parietal association area [3]. FDG-PET detects decreased glucose metabolism and is more sensitive than cerebral blood flow SPECT, but this examination is not covered by medical insurance in Japan [4]. In dementia with Lewy bodies, disturbance of cardiac sympathetic nerve causes a decrease in MIBG uptake on MIBG scintigraphy [5]. Dopamine transporter scintigraphy using ^{123}I-FP-CIT is considered to reflect the density of dopamine transporter in the striatum. This test is approved for health insurance coverage in Japan for differentiating between dementia with Lewy bodies and Alzheimer's disease dementia, and is increasingly being used clinically.

For molecular imaging, techniques for visualizing amyloid β (Aβ) and tau have been established [6]. ^{11}C-PIB, ^{18}F-Florbetapir, ^{18}F-Flutemetamol, and ^{18}F-Florbetaben have been developed as ligands targeting Aβ [7]. Refer to CQ6-6 for the clinical significance of amyloid PET testing. ^{11}C-PBB3 and ^{18}F-T807 have been developed as ligands for visualizing tau. These techniques are mainly used for research purposes, and currently they are not covered by health insurance in Japan.

References

1) Filippi M, Agosta F, Barkhof F, et al. EFNS task force: the use of neuroimaging in the diagnosis of dementia. Eur J Neurol. 2012; 19(12): e131-e140.
2) Harper L, Barkhof F, Scheltens P, et al. An algorithmic approach to structural imaging in dementia. J Neurol Neurosurg Psychiatry. 2014; 85(6): 692-698.
3) Yeo JM, Lim X, Khan Z, et al. Systematic review of the diagnostic utility of SPECT imaging in dementia. Eur Arch Psychiatry Clin Neurosci. 2013; 263(7): 539-552.
4) Shivamurthy VK, Tahari AK, Marcus C, et al. Brain FDG PET and the diagnosis of dementia. AJR Am J Roentgenol. 2015; 204(1): W76-W85.
5) King AE, Mintz J, Royall DR. Meta-analysis of 123I-MIBG cardiac scintigraphy for the diagnosis of Lewy body-related disorders. Mov Disord. 2011; 26(7): 1218-1224.
6) Pearson SD, Ollendorf DA, Colby JA. Amyloid-β positron emission tomography in the diagnostic evaluation of Alzheimer disease: summary of primary findings and conclusions. JAMA Intern Med. 2014; 174(1): 133-134.
7) Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013; 9(4): e106-e109.

Search formula

PubMed search: July 1, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Diagnostic Imaging" [Majr] OR imaging [TI] OR neuroimaging [TI] OR MRI [TI] OR CT [TI] OR SPECT [TI] OR PET [TI]OR MIBG [TI])

Ichushi search: July 1, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)OR Diagnosis/TH OR Diagnosis/TI AND (Diagnostic imaging/MTH or Imaging/TI or MRI/TI and CT/TI or SPECT/TI or PET/TI or MIBG/TI)

CQ 2-9

What are the useful blood and cerebrospinal fluid tests for the diagnosis of dementia?

Answer

Blood tests are done to identify dementia associated with medical diseases. No useful blood tests for identifying degenerative dementia have been established. Cerebrospinal fluid examination is used to exclude infections, tumors, and inflammatory disorders in the central nervous system. Decreased amyloid β42 (Aβ42) and elevated phosphorylated tau in cerebrospinal fluid have been reported in Alzheimer's disease dementia. B

Comment and evidence

Blood tests are recommended to diagnose dementia and detect cognitive decline associated with medical diseases. Blood counts, hematology and blood biochemistry, and measurements of thyroid hormone, electrolytes, fasting blood glucose, vitamin B_{12}, and folic acid are recommended. Serological tests for syphilis and human immunodeficiency virus (HIV) are performed when such diagnoses are suspected based on medical history [1].

Cerebrospinal fluid examination is performed in atypical cases and other cases in which dementia subtype is difficult to diagnose [2]. General examination and cytology are used to exclude infections, tumors (malignant lymphoma and metastatic tumors), and inflammatory diseases in the central nervous system.

Alzheimer's disease dementia manifests decrease in amyloid β42 (Aβ42) peptide and increases in total tau and phosphorylated tau proteins. The decrease in Aβ42 in cerebrospinal fluid is thought to reflect the accumulation of Aβ in the brain and correlates with the results of amyloid positron emission tomography (PET) [3]. These biomarkers have been incorporated into various diagnostic criteria for Alzheimer's disease dementia [International Working Group (IWG)-2 criteria [4] and National Institute on Aging–Alzheimer's Association workgroup (NIA-AA) diagnostic criteria [5]]. As a supplementary diagnostic test for dementia, phosphorylated tau measurement is covered by health insurance in Japan. However, Aβ42 measurement is not covered by insurance. Mild cognitive impairment that converts to Alzheimer's disease dementia has been reported to show decrease in Aβ42 and increases in total tau and phosphorylated tau [1, 2].

According to a meta-analysis, α-synuclein in cerebrospinal fluid is lower in dementia with Lewy bodies compared to Alzheimer's disease dementia, but this biomarker has not been applied to clinical use [6]. Biomarkers for frontotemporal lobar degeneration are also in the stage of development and none have been applied to clinical use. Measurement of total tau in cerebrospinal fluid as a supplementary diagnostic test for Creutzfeldt-Jakob disease is covered by health insurance in Japan.

References

1) Ahmed RM, Paterson RW, Warren JD, et al. Biomarkers in dementia: clinical utility and new directions. J Neurol Neurosurg Psychiatry. 2014; 85(12): 1426-1434.
2) Noel-Storr AH, Flicker L, Ritchie CW, et al. Systematic review of the body of evidence for the use of biomarkers in the diagnosis of dementia. Alzheimers Dement. 2013; 9(3): e96-e105.
3) van Harten AC, Kester MI, Visser PJ, et al. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. Clin Chem Lab Med. 2011; 49(3): 353-366.
4) Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014; 13(6): 614-629.
5) McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-269.
6) Lim X, Yeo JM, Green A, et al. The diagnostic utility of cerebrospinal fluid alpha-synuclein analysis in dementia with Lewy bodies—a systematic review and meta-analysis. Parkinsonism Relat Disord. 2013; 19(10): 851-858.

Search formula

PubMed search: July 1, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis[TI]OR diagnoses [TI] OR diagnostic [TI]))) AND ("Biological Markers" [Majr] OR biological marker* [TI] OR biomarker* [TI] OR "Hematologic Tests" [Mesh] OR hematologic test* [TI] OR blood test* [TI] OR "Cerebrospinal Fluid" [Mesh] OR "cerebrospinal fluid" [TI] OR "cerebrospinal fluid" [SH])

Ichushi search: July 1, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Biological marker/MTH OR Biological marker/TI OR Biomarker/TI OR Hematological test/TH OR Hematological test/TI OR Blood test/TI OR Cerebrospinal fluid test/TH OR Cerebrospinal fluid test/TI)

CQ 2-10

Which physical and neurological findings require attention when diagnosing dementia?

Answer

Physical and neurological examinations are performed in the process of diagnosing dementia. Findings from physical examination may lead to a diagnosis of treatable dementia associated with medical disorders. Findings obtained from neurological examinations are useful in the diagnosis of different types of degenerative dementia.

Comment and evidence

Physical and neurological examinations are performed as the first step in the diagnosis of dementia [1].

Physical examinations include (1) hair, skin; (2) palpebral conjunctiva, pupil; (3) oral mucosa, pharynx, tongue; (4) neck: lymph nodes, thyroid gland, auscultation of vascular murmur; (5) pulse and blood pressure; (6) chest; (7) abdomen; (8) extremities: skin, joints, check for edema [1]. Cervical vascular murmur and pulse irregularity suggest the presence of cerebrovascular lesions. Pay attention to the presence or absence of otolaryngologic disorders accompanied by hearing impairment. Alopecia, thyroid swelling, and non-pitting edema in the lower extremities are found in hypothyroidism. Erythema nodosum, oral aphtha, and genital ulcer are findings of *neuro-Behçet's disease*. Asterixis is observed in hepatic encephalopathy.

Neurological examinations include investigations of the (1) level of consciousness; (2) cognitive function tests; (3) cranial nerves, (4) motor system of extremities; (5) deep tendon reflex and pathological reflex; (6) involuntary movement; (7) sensory system; (8) posture/gait; and (9) autonomic nervous system [2, 3].

The presence or absence of impaired consciousness is required to differentiate dementia from delirium. The presence of semi-blindness (hemianopsia) may suggest cerebrovascular lesions in the brain. If observation of the fundus using an ophthalmoscope reveals optic disc edema, the presence of intracranial lesion causing increased intracranial pressure should be suspected. Finding of weakened light reflex but preserved convergence reflex (Argyll Robertson pupil) is a symptom of suspected neurosyphilis. Impairment of vertical eye movement is seen at high frequency in progressive supranuclear palsy. Restricted eye movement and diplopia are observed in Wernicke encephalopathy. Limb-kinetic apraxia and ideomotor apraxia are characteristics of corticobasal degeneration. Tongue atrophy and fasciculation are observed in dementia associated with motor neuron disorder. Chorea is observed in Huntington's disease and dentatorubral-pallidoluysian atrophy (DRPLA). Resting tremor is found in dementia with Lewy bodies and Parkinson's disease. Myoclonus is manifested in Creutzfeldt-Jakob disease, corticobasal degeneration, Alzheimer's disease dementia, and others. Frontal lobe signs such as grasp reflex and suck reflex are observed in patients with frontotemporal lobar degeneration. Sensory disturbances in distal extremities occur in patients with peripheral neuropathy due to vitamin B_{12} deficiency. Deep sensory impairment is observed in tabes dorsalis due to neurosyphilis and subacute combined degeneration of the spinal cord. Shuffling gait and freezing gait are characteristics of dementia with Lewy bodies. Shuffling wide-based gait is seen in normal pressure hydrocephalus. Autonomic dysfunction such as orthostatic hypotension, dysuria, and constipation are observed in dementia with Lewy bodies [4].

References

1) Ames D, Burns A, O'Brien J (Eds.). Dementia, fourth edition. Boca Raton, Fl: CRC Press; 2010.
2) Mizuno M. Handbook of Neurosurgical: Differential Diagnosis and Treatment, 4th edition. Tokyo: Igaku Shoin; 2010. (In Japanese)
3) Shibazaki H. For Persons Learning Neurological Diagnosis, 2nd edition. Tokyo: Igaku Shoin; 2013. (In Japanese)
4) Idiaquez J, Roman GC. Autonomic dysfunction in neurodegenerative dementias. J Neurol Sci. 2011; 305(1-2): 22-27.

Search formula

PubMed search: July 1, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia[TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Physical Examination" [Mesh] OR physical examination* [TI] OR physical finding*[TI])

Ichushi search: July 1, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Physiological test/MTH OR Physiological test/TI OR Physical findings/TI)

CQ 2-11

What are the drugs that affect the diagnosis of dementia?

Recommendations

It is necessary to keep in mind the possibility that drug-induced effects may underlie the decline in cognitive function. Therefore, confirm the medications taken by the patients. Drug-induced cognitive impairment is more likely to occur when the patients are of advanced age, have hepatic or renal dysfunction, or are taking multi-drug combination. Apart from causing delirium, drugs may induce cognitive impairment with a latent or subacute course. Anticholinergics and benzodiazepines are risk factors of cognitive impairment and dementia. 1B

Comment and evidence

Drug-induced cognitive impairment has the following characteristics [1-2]: (1) decreased attention is prominent; (2) drug-induced cognitive impairment changes over time; (3) patient may manifest symptoms resembling delirium; (4) cognitive impairment improves by discontinuing drug use; and (5) cognitive function deteriorates by drug overdose. Drug-induced cognitive impairment occurs more commonly in patients with advanced age, hepatic or renal dysfunction, or are taking multi-drug combination.

Among patients who show cognitive impairment, 2-12% is estimated to be associated with drugs [1]. It should also be kept in mind that some drugs cause delirium. One report shows that delirium is related to drugs in 11-30% of hospitalized older patients [1].

Some drug classes tend to induce cognitive impairment. Among psychotropic drugs, phenothiazine antipsychotics with anticholinergic effects, benzodiazepines that are anxiolytics, and tricyclic antidepressants more readily induce cognitive impairment. Anti-parkinsonian drugs, opioid analgesics, NSAIDs and corticosteroids are drugs with a potential to induce cognitive impairment. Attention should also be paid to the following drugs: drugs for the cardiovascular system including some anti-hypertensive drugs, anti-arrhythmic drugs, digitalis, and diuretics; antibacterial and antiviral drugs; antitumor drugs; drugs for overactive bladder and drugs for asthma with anticholinergic effects; and drugs for the digestive system with anti-histamine effect.

Anticholinergic drugs used in older persons have been reported to increase the risk of cognitive decline and development of dementia [3]. Cognitive impairment caused by anti-cholinergic drugs includes reduced memory, impaired attention, and delirium, and is particularly common in older persons [4].

Cognitive impairment caused by long-term use of benzodiazepines includes impaired spatial perception, impaired verbal memory, and attention deficits. A meta-analysis reports that taking oral benzodiazepines is a risk of dementia [5].

The Beers criteria clearly define appropriate drug prescriptions, created for the purpose of correcting inappropriate multi-drug combinations and avoiding overdosage in older patients [6]. In addition, the "Guidelines for Medical Therapy and its Safety in the Elderly 2015" was published by the Japan Geriatrics Society [7]. Refer to this reference when prescribing for older patients. In addition, it is possible to browse the package inserts of pharmaceuticals from the website of the Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp/) and search for adverse events of individual drugs [8].

References

1) Moore AR, O'Keefe ST. Drug-induced cognitive impairment in the elderly. Drugs Aging. 1999; 15(1); 15-28.
2) Shinohara M, Yamada M. Cognitive impairment caused by drugs. Brain Nerve. 2012; 64(12); 1405-1410.
3) Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population; the 3-city study. Arch Intern Med. 2009; 169(14): 1317-1324.
4) Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008; 168(5); 508-513.
5) Zhong G, Wang Y, Zhang Y, et al. Association between benzodiazepine use and dementia; A meta-analysis. PLoS One. 2015; 10(5): e0127836.
6) Campanelli CM. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012; 60: 616-631.
7) Japan Geriatrics Society, Japan Agency for Medical Research and Development / Study Group on Safety of Medical Treatment in the Elderly (Ed.) Guidelines for Medical Treatment and its Safety in the Elderly 2015. Tokyo; Medical Tribune; 2015. (In Japanese)
8) Pharmaceuticals and Medical Devices Agency, Information in Package Insert of Pharmaceuticals. http://www.info.pmda.go.jp/psearch/html/menu_tenpu_base.html (In Japanese)

Search formula

PubMed search: July 1, 2015 (Wednesday)

#1 ("Dementia/diagnosis" [Majr] OR (dementia[TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic[TI]))) AND ("Physiological Effects of Drugs" [Mesh] OR "Pharmacologic Actions/adverse effects" [Mesh] OR ("Chemicals and Drugs Category" [Majr] AND "adverse effects" [SH]))

Ichushi search: July 1, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)OR Diagnosis/TH OR Diagnosis/TI) AND ((SH = Toxicity/side effect, chemical induction, adverse effect)OR Substance-related impairment /TH OR physiological action of drug/MTH)

CQ 2-12

Are there useful genetic tests for the diagnosis of dementia?

Answer

For hereditary dementia with Mendelian mode of inheritance, the causative genes have been identified, and a definitive diagnosis can be established by identifying the gene mutation. Genetic diagnosis in principle requires patient's consent and should not be coerced. Provide genetic counseling as necessary. APOE polymorphism is a genetic factor of Alzheimer's disease dementia. and the frequency of carrier of the *APOE* ε4 allele is significantly higher in individuals with Alzheimer's disease dementia. Use of *APOE* polymorphism as a supplementary diagnostic test for Alzheimer's disease dementia is not recommended.

Comment and evidence

The causative genes of familial dementia that show Mendelian inheritance pattern have been identified. A diagnosis is established when a pathological mutation in the causative gene is identified. Mutations in *APP*, *PSEN1*, and *PSEN2* are known to cause familial Alzheimer's disease, and more than 100 cases have been reported in Japan [1]. Familial Alzheimer's disease associated with genetic mutations often develops in the 40s and 50s [1, 2]. The genetic causes of familial Lewy body dementia include *SNCA* missense mutation and duplication mutation. Several genes responsible for frontotemporal lobar degeneration (FTLD) have been reported [3]. In Japan, hereditary FTLD is associated frequently with *MAPT* mutations, and rarely with *GRN* mutations [1].

APOE is a susceptibility gene for Alzheimer's disease dementia, and polymorphisms of this gene influence the susceptibility of an individual to the disease [4]. The frequency of ε4 allele of *APOE* is high in Alzheimer's disease dementia. According to an analysis of a larger number of Japanese patients, *APOE* ε4 allele is positive in approximately one-half of the patients with Alzheimer's disease dementia. Testing the *APOE* polymorphism as a supplementary diagnostic test for Alzheimer's disease dementia is not recommended [5]. Genome-wide association studies in a large-scale sample of Alzheimer's disease dementia identifies 19 significant susceptibility genes, but the odds ratios are not high [6].

Genetic diagnosis in principle requires patient's consent and should not be coerced [7]. Consideration should be given to the patient's psychological burden of being diagnosed with a hereditary disease through genetic diagnosis, and the impact on the patient's family. Consider to provide opportunities for genetic counseling as needed.

References

1) Kasuga K, Kikuchi M, Tokutake T, et al. Systematic review and meta-analysis of Japanese familial Alzheimer's disease and FTDP-17. J Hum Genet. 2015; 60(5): 281-283.
2) Bettens K, Sleegers K, Van Broeckhoven C. Genetic insights in Alzheimer's disease. Lancet Neurol. 2013; 12(1): 92-104.
3) Pelicano Paulos J, Massano J. Clinical, genetic and neuropathological features of frontotemporal dementia: an update and guide. Acta Med Port. 2013; 26(4): 392-401.
4) Schellenberg GD, Montine TJ. The genetics and neuropathology of Alzheimer's disease. Acta Neuropathol. 2012; 124(13): 305-323.
5) Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011; 13(6): 597-605.
6) Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013; 45(12): 1452-1458.
7) "Guidelines on Genetic Diagnosis of Neurological Diseases" Preparation Committee (Ed.). Japanese Society of Neurology (Supervision). Guidelines on Genetic Diagnosis of Neurological Diseases 2009. Tokyo: Igaku Shoin; 2009. (In Japanese)

Search formula

PubMed search: July 1, 2015 (Wednesday)
#1 ("Dementia/diagnosis" [Majr] OR (dementia [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Genetic Testing" [Mesh] OR "Heterozygote Detection" [Mesh] OR "Genetic Predisposition to Disease" [Mesh] OR "Molecular Diagnostic Techniques" [Mesh] OR "Mutation" [Majr] OR genetic test* OR genetic diagnosis* OR mutation [TI])

Ichushi search: July 1, 2015 (Wednesday)
#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Genetic testing/TH OR Genetic testing/TI OR Gene testing/TI OR Gene diagnosis/TI OR Gene analysis/TI OR Gene analysis/TI)