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Original Article

The National Center for Geriatrics and Gerontology Diagnostic Reference Tool for Degenerative Dementia (NCGG-4D): A simple and effective tool

Masashi Tsujimoto[1], Akiko Yamaoka[1], Kentarou Horibe[1], Akinori Takeda[1], Yutaka Arahata[1], Takashi Sakurai[2], *Yukihiko Washimi[1]

[1]Department of Cognitive Disorders, National Center for Geriatrics & Gerontology, Obu, Aichi, Japan
[2]Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics & Gerontology, Obu, Aichi, Japan

ABSTRACT

Background/Purpose: As the number of people with dementia is increasing because of the aging society, efficient reference tools are needed, because symptoms vary between individuals Herein, we have invented a simple and effective reference tool. The main aim of this tool is to act as a guide of the symptoms essential for dementia diagnosis, in order to suggest a possible diagnosis, which can prompt the next evaluation step, such as referral to specific hospitals or institutions.

Methods: The National Center for Geriatrics and Gerontology Differential Diagnostic Reference Tool for Degenerative Dementia (NCGG-4D) was developed in accordance with the international criteria of dementia diseases, such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), among others. In order to evaluate the usefulness of this tool, we compared the validity of this tool to clinical diagnoses.

Results: The NCGG-4D showed highest sensitivity for DLB (0.813, 95% CI=0.665–0.908), while specificity for all diseases was above 0.80 (MCI: 0.824, 95% CI=0.804–0.842; AD: 0.866, 95% CI=0.840–0.889; DLB: 0.961, 95% CI=0.954–0.965; bvFTD: 0.990, 95% CI=0.987–0.994). The highest positive predictive value was for AD (0.775, 95% CI=0.730–0.813).

Conclusion: The NCGG-4D highlighted the symptoms essential for a practical diagnosis of dementia. This may be an useful evaluation tool for dementia diagnosis.

***Correspondence**
Yukihiko Washimi
National Center for Geriatrics & Gerontology, Obu, Aichi, Japan
E-mail:
washimi@ncgg.go.jp

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INTRODUCTION

In our aging society, dementia represents a major public health problem. In 2013, the number of people living with dementia worldwide was estimated to be 44.35 million, a figure that has been predicted to reach 75.62 million in 2030 and 135.46 million in 2050.[1] As the number of individuals with dementia is increasing, it may be inferred that the rates for not detecting dementia vary considerably worldwide.[2] Thus, screening for dementia at a primary care level is an optimal and crucial strategy.[3] However, this is hindered by the complicated evaluations required for making a diagnosis.[4]

There are currently various tools that can be used to screen for and evaluate the symptoms of dementia. The most widely used screening test is the Mini-Mental State Examination (MMSE)[5] and the Montreal Cognitive Assessment (MoCA),[6] which are used for estimating

the severity of cognitive impairment. Furthermore, various other popular measures for evaluating the possible presence of dementia are available, including the Clock Drawing Test[7] and the Six-Item Cognitive Impairment Test.[8] There are also detailed scales for evaluating the severity of dementia, such as the Clinical Dementia Rating[9] and the Functional Assessment Staging.[10] However, these are additional tests or screening batteries that are administered after documenting the disease history and recording essential symptoms for making a diagnosis. Thus, it takes additional time to administer these kinds of tests, and in practice, clinicians' time constraints have to be taken into consideration. Additionally, there is no satisfactory tool for assessing numerous patients' symptoms effectively at a primary care level. Moreover, repeated evaluation is also crucial for dementia assessment, because it is typically difficult to diagnose dementia at the first visit, even for expert physicians, and particularly for non-Alzheimer disease (AD) forms of dementia.[11] Therefore, symptoms should be assessed regularly in order to make the correct diagnosis.

Given the above, family physicians would greatly benefit from a simple and efficient tool that could act as a guide for screening and evaluating patients for dementia. We developed and assessed a tool that can assist in the evaluation of patients with dementia.

METHODS

This study was approved by the Medical Ethics Committee of the National Center for Geriatrics and Gerontology. All data were stored and analyzed in such a way as to take care to preserve the subjects' anonymity.

Diagnostic tool: The National Center for Geriatrics and Gerontology Differential Diagnostic Tool for Degenerative Dementia (NCGG-4D)

We developed a tool, termed the National Center for Geriatrics and Gerontology Differential Diagnostic Tool for Degenerative Dementia (NCGG-4D), which has two components: the NCGG-4D questionnaire for caregivers (Table 1), and the NCGG-4D questionnaire for doctors (Table 2). As shown in Table 1, the questionnaire for caregivers is based on the criteria for dementia with Lewy bodies (DLB)[12] and behavioral variant fronto-temporal disease (bvFTD).[13,14] Table 1 also shows how each question is directly connected to our diagnostic program. For example, item 1 of the caregiver questionnaire is connected to item 8 of the NCGG-4D doctor's questionnaire.

Each question of the NCGG-4D doctor's questionnaire was developed based on various international criteria for several diseases, including mild cognitive impairment (MCI), AD, DLB, and bvFTD. The MCI criteria were taken from the Petersen criteria[15] and the National Institute on Aging-Alzheimer's Association workgroups.[16] The AD criteria were taken from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[17] as well as criteria from workgroups of the National Institute of Neurological and Communicative Disease and the Stroke/Alzheimer's Disease and Related Disorders Association,[18] and the National Institute on Aging-Alzheimer's Association.[19] The DLB criteria were taken from the international workshop criteria of the DLB Consortium.[12] Finally, the bvFTD criteria were taken from the revised International Behavioural Variant Frontotemporal Dementia Criteria Consortium.[13,14] The questions of the NCGG-4D doctor's questionnaire (Table 2) relate to particular diseases: MCI, questions 1–4; AD, questions 1–6; DLB, questions 1, 3, 7–11; and bvFTD, questions 12–16. Considering the answers to these questions, the software indicates a candidate diagnosis. For example, the algorithms in the various conditions were as follows. In the case of MCI, the answer to questions 1 and 2 are both No, the answer to question 4 is Yes, and the answers to one of the questions among questions 3a-d is Yes. In the case of AD, the answers to questions 1, 5, and 6 are all Yes, the answer question 2 is No, the answer to 3-a is Yes, and the answers to two or more questions among 3-b-g are Yes. When questions 1, 3, 7, 8, and 9 are responded to with Yes, the candidate diagnosis is DLB. For bvFTD, the answer to 5 is Yes, and more than two of the questions among 11-15 are answered as Yes.

Some questions are difficult to evaluate or can result in a different assessment outcome, because of question ambiguity. Specifically, these include some practically assessable questions related to visuospatial ability, apraxia, agnosia, and parkinsonism, which should facilitate the assessment, and ensure a unified assessment method. Nonetheless, these practically assessable reference questions may sometimes not be sufficient for a complete evaluation. For cases that are difficult to evaluate, "unknown" is assigned.

When using this tool, the first step was for caregivers to fill out the NCGG-4D questionnaire for caregivers, before consulting the doctor (Table 1). The aim of this step was to identify symptoms efficiently. The answers to these questions are connected to each question in the NCGG-4D doctor's questionnaire (Table 2). As the next step, doctors then evaluated each symptom in accordance with the NCGG-

Question number in Table 1	Related number in the diagnostic program in Table 2
1	8)
2	10)
3	11)
4–6	12)
7, 8	13)
9, 10	14)
11–13	15)
14–16	16)

The answer to each question was connected to the diagnostic program shown in Table 2.

Table 1. The NCGG-4D questionnaire for caregivers

Mark YES if the following symptoms are present.

1. Visual hallucinations, seeing something that should not be there ☐YES ☐NO

2. Vocalizing, moving around, sometimes violently, while sleeping ☐YES ☐NO

3. Severe neuroleptic sensitivity, i.e., sensitive to antipsychotic medicine ☐YES ☐NO ☐Unknown

4. Altered food preferences, e.g., change in food habits (craving sweets/carbohydrates, etc.) ☐YES ☐NO

5. Binge eating, increased consumption of alcohol or cigarettes, e.g., eating excessive amounts of food despite acknowledging satiety, or excessive alcohol intake ☐YES ☐NO

6. Oral exploration, e.g., chewing or ingestion of inedible objects ☐YES ☐NO

Mark YES if the following symptoms appear within the first 3 years from the onset of dementia.

7. Apathy, e.g., loss of motivation to work or take part in hobbies ☐YES ☐NO

8. Inertia, e.g., requires specific direction to start or finish daily activities, such as brushing teeth ☐YES ☐NO

9. Diminished responsiveness to other people's needs and feelings, e.g., hurtful comments, causing others pain or distress ☐YES ☐NO

10. Diminished social interest, interrelatedness or personal warmth, e.g., relatives and friends experience the patient as uncharacteristically distant (no longer touches, hugs or seeks out their company) ☐YES ☐NO

11. Simple repetitive movements, e.g., tapping, clapping, scratching continuously ☐YES ☐NO

12. Complex, compulsive or ritualistic behaviors, e.g., repetitive trips to the bathroom (without need) or walking fixed routes ☐YES ☐NO

13. Stereotypical speech, e.g., habitually repeats words or phrases despite their lack of communicative value ☐YES ☐NO

14. Socially inappropriate behavior, e.g., public nudity or urination, or inappropriately approaching others (touching or kissing strangers, etc.) ☐YES ☐NO

15. Loss of manners or decorum, e.g., inappropriate laughter, cursing, or loudness ☐YES ☐NO

16. Impulsive, rash or careless actions, e.g., reckless driving, new-onset gambling, or buying or selling objects without regard for consequences ☐YES ☐NO

Table 2. The National Center for Geriatrics and Gerontology Differential Diagnostic Tool for Degenerative Dementia (NCGG-4D) for doctors

1) Dysfunction at work or during everyday activities	☐YES ☐NO
2) Delirium, major psychiatric problems or loss of consciousness	☐YES ☐NO ☐Unknown
3) Impaired functions	
a) Memory impairment	☐YES ☐NO ☐Unknown
b) Executive dysfunction	☐YES ☐NO ☐Unknown
c) Language dysfunction	☐YES ☐NO ☐Unknown
d) Personality change	☐YES ☐NO ☐Unknown
e) Visuospatial disabilities (the line bisection test)	☐YES ☐NO ☐Unknown
f) Apraxia: Fox shaping (ideomotor apraxia); taking off and putting on a jacket (dressing apraxia); finger tapping (limb-kinetic apraxia)	☐YES ☐NO ☐Unknown
g) Agnosia: Raise right hand (right-left disorientation); show index finger (finger agnosia)	☐YES ☐NO ☐Unknown
4) History-taken from caregivers	☐YES ☐NO
5) Gradual onset over months to years	☐YES ☐NO
6) Clear-cut decline in cognitive function	☐YES ☐NO
7) Fluctuating symptoms during the day	☐YES ☐NO
8) Recurrent visual hallucinations	☐YES ☐NO
9) Parkinsonism	☐YES ☐NO
a) Rigidity (neck and limbs)	☐YES ☐NO
b) Tremor (limb tremor at rest)	☐YES ☐NO
c) Bradykinesia (pronation and supination of hands)	☐YES ☐NO
d) Duration between the onset of dementia and parkinsonism:	☐Within 1 year ☐Over 1 year ☐Unknown
10) REM sleep behavior disorder	☐YES ☐NO ☐Unknown
11) Severe neuroleptic sensitivity	☐YES ☐NO ☐Unknown
12) Hyperorality and dietary changes	☐YES ☐NO

The following questions refer to symptoms experienced within the first 3 years from onset:

13) Apathy or inertia	☐YES ☐NO
14) Loss of sympathy or empathy	☐YES ☐NO
15) Perseverative, stereotyped or compulsive/ritualistic behavior	☐YES ☐NO
16) Behavioral disinhibition	☐YES ☐NO

4D doctor's questionnaire (Table 2), referring to the answer to the relevant question in the caregivers' questionnaire (Table 1). Subsequently, based on these answers, a putative diagnosis is selected.

Validation of the NCGG-4D

In order to evaluate the effectiveness of this reference tool, the difference between the diagnosis results obtained using the tool and a non-NCGG-4D-based clinical evaluation were compared. The sensitivity and specificity of the NCGG-4D were examined for diagnosis of MCI, AD, DLB and bvFTD were examined.

We recruited consecutive outpatients at the Center for Comprehensive Care and Research for Memory Disorders of the National Center for Geriatrics and Gerontology, Aichi, Japan, between January 2012 and July 2015, to participate in our study. In total, 717 patients participated in the study (male=274, female=443). All participants underwent the following evaluations: 1) laboratory analyses: complete blood count, chemistry, vitamin B_{12}/folate, syphilis serology, and thyroid function tests; 2) neuroimaging: 1.5-T MRI and single photon emission computed tomography (SPECT); and 3) neuropsychological tests conducted by clinical psychologists. Based on these examinations, two or more experienced neurologists, psychiatrists, and/or geriatricians provided a diagnosis. The NCGG-4D was also administered prior to these evaluations. To validate the tool, we compared the diagnosis derived by implementing the software based on the answers to the questions in the tool, with the diagnosis based on non-NCGG-4D-based clinical evaluations.

Statistical analyses

We conducted descriptive analyses on demographic and clinical features, presenting results as the mean and 95% confidence intervals [CI] for quantitative variables, and the number and percentage for qualitative variables. We calculated the sensitivity, specificity, and positive- and negative-predictive values as a diagnostic measurement for each category, by comparing NCGG-4D diagnoses with the non-NCGG-4D-based clinical diagnoses. All the data management and statistical analyses were performed using SPSS 20.0 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Table 3 shows the demographic data for all 717 cases (number, sex, age, education, and MMSE score), as well as data for each dementia subtype (MCI, AD, DLB, bvFTD, and "other") as diagnosed by the doctor. The category "other" included patients diagnosed with psychosomatic disease (n=16), vascular dementia (n=16), normal pressure hydrocephalus (n=9), epilepsy (n=6), metabolic disease (n=6), stroke (n=6), neurodegenerative disease (n=5), and drug-induced dementia (n=3), as well as those identified as healthy (n=86) or undiagnosed (n=35). Overall, AD had the highest incidence (41%, n=294).

To validate the NCGG-4D, we compared the diagnoses obtained using the NCGG-4D with the clinical diagnoses. The sensitivity, specificity, positive-predictive value, and negative-predictive values for each type of dementia are shown in Table 4.

DLB was diagnosed with the highest sensitivity (0.813, 95% CI=0.665–0.908). Specificity for all diseases was above 0.80 (MCI: 0.824, 95% CI=0.804–0.842; AD: 0.866, 95% CI=0.840–0.889; DLB: 0.961, 95% CI=0.954–0.965; bvFTD: 0.990, 95% CI=0.987–0.994). The highest positive predictive value was for AD (0.775, 95% CI=0.730–0.813). All of these disease categories also had a high negative predictive value, which was approximately 80% or more (MCI: 0.879, 95% CI=0.857–0.898; AD: 0.793, 95% CI= 0.770–0.814; DLB: 0.991, 95% CI=0.984–0.996; bvFTD: 0.990, 95% CI=0.987–0.994).

DISCUSSION

In this study, we developed and validated a diagnostic reference tool for dementia, the NCGG-4D, which focuses on patients' symptoms. Our main aim in developing this tool was to provide a guide for facilitating evaluation. Our tool consists of questions that evaluate specific symptoms for each dementia type, which allows it to be used as a referral tool. The NCGG-4D differs from previous tools in that it refers to the symptoms essential for the diagnosis of dementia disorders simply and effectively. As such, the tool will help to overcome some of the major barriers encountered by family physicians, who are not dementia specialists, including the complicated symptom evaluations typically required for diagnosis. In addition, the time required for evaluation is shortened markedly with our tool because it provides an evaluation reference and a questionnaire filled out by caregivers before the patient visits the doctor. Thus, considerably less time is required for the family physician to make a preliminary diagnosis.

Nevertheless, detailed evaluations, including neuroimaging and neuropsychological testing, allow patients to be diagnosed accurately. For example, brain imaging techniques, such as SPECT,[20] and positron-emission tomography[21] can diagnose AD with a sensitivity and specificity of up to 80–90%. When neuroimaging results are considered alongside neuropsychological test results, diagnostic accuracy is further increased.[22] Considering the above, it is perhaps not unexpected that the results from the NCGG-4D are not superior to those of these detailed examinations, as the software does not incorporate neuroimaging or neuropsychological testing results. We also incorporated the symptoms of four diseases, i.e., MCI, AD, DLB, and bvFTD, into our software, as family physicians are likely to be presented with a variety of symptoms, but may not have access to specialist knowledge or resources. Furthermore, we intend to include additional items to evaluate gait disturbance and other characteristic symptoms of these diseases in the tool in future.

We also avoided making use of the complicated evaluations

usually required for diagnosis; rather, the questions used in our tool are based on international criteria for the major dementia disorders. This will make it possible for family physicians to evaluate dementia symptoms repeatedly in a consistent manner over a period of time, using our tool as the requisite minimum approach. That is, regular use of the NCGG-4D would make it possible to detect changes in symptoms early on, in a systematic manner. Given that misdiagnosis, even by expert physicians, is common,[11] longitudinal evaluation is vital for an accurate and early diagnosis. In addition, some diagnoses may change depending on later symptoms. In such cases, regular assessment is also crucial, even after a clinical diagnosis, and a tool such as ours could facilitate this.

It is also being recognized that dementia in older people arises from multiple pathogeneses, such as brain stroke and AD. Pure dementia, from a single disease origin, is less common. Therefore, the first dementia diagnosis may be partly or completely wrong. This further underscores the need for regular evaluation of symptoms, even after clinical diagnosis. In that case, our tool is useful, because the same evaluation system can be used to compare changes in symptoms. Moreover, from the viewpoint of dementia cohort research, the long-term progressive nature of the disease and potential changes in doctors and places of habitation make it difficult to collect longitudinal data in order to compile a longitudinal symptom database. Hence, if a common tool could be used by both family physicians and special hospital units, it would greatly facilitate cohort studies of dementia.

This study was the first step in the development of such a tool, and we only evaluated it at a specialized hospital. We next intend to evaluate the usefulness of this tool at the primary care level. We also plan to analyze the factors or symptoms that are responsible for the differences observed between the software's diagnoses and the clinical diagnoses. By increasing the number of patients, we hope to be able to identify the point at which it is necessary to refer patients for evaluation using neuroimaging or psychological tests, based on the outcomes derived using our diagnostic tool. Nonetheless, even without detailed neuroimaging and neuropsychological tests, our tool displayed good sensitivity for diagnosing DLB. This result should be confirmed in a larger sample, as the small number of DLB and bvFTD cases in the present study could limit the interpretation of these results.

In conclusion, we have developed and validated the NCGG-4D, a simple and effective tool for identifying patients who should be referred for clinical evaluation for diagnosis. Our tool represented an improvement on previous tools in terms of its ability to aid in direct referral of patients to appropriate hospitals. With this tool, the criteria for each dementia disorder can be checked and patients' symptoms can be systematically evaluated. If this tool comes into common use by physicians from various specialties for evaluation of patients on a regular basis, it will be possible not only to determine longitudinal symptom changes, but also to use the tool as a method of referral to specialized hospitals or care homes.

CONFLICTS OF INTEREST STATEMENT

No potential conflicts of interest were disclosed.

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Table 3. Demographic data of all participants according to dementia type

	Total	MCI	AD	DLB	bvFTD	Other
n	717	191	294	32	12	188
Sex (% female)	61.79	58.11	67.69	59.38	50	57.45
Age, years	76.79 (8.67)	76.79 (7.20)	78.65 (7.45)	81.25 (6.80)	71.08 (7.39)	73.47 (10.73)
Education, years	10.57 (2.83)	10.88 (2.66)	9.95 (2.74)	9.23 (2.49)	11.83 (2.98)	11.33 (2.90)
MMSE score	21.07 (5.71)	23.89 (3.51)	17.93 (4.88)	17.13 (5.43)	17.82 (9.00)	23.97 (5.52)

Data are presented as mean (SD) or %. MCI=mild cognitive impairment; AD=Alzheimer's disease; DLB=dementia with Lewy bodies; bvFTD=behavior variant fronto-temporal disease.

Table 4. The value of "NCGG-4D diagnosis" vs. "doctor's diagnosis"

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
MCI	0.684 (0.629–0.735)	0.824 (0.804–0.842)	0.583 (0.536–0.626)	0.879 (0.857–0.898)
AD	0.671 (0.634–0.705)	0.866 (0.840–0.889)	0.775 (0.732–0.813)	0.793 (0.770–0.814)
DLB	0.813 (0.665–0.908)	0.961 (0.954–0.965)	0.491 (0.402–0.548)	0.991 (0.984–0.996)
bvFTD	0.417 (0.208–0.63)	0.990 (0.987–0.994)	0.417 (0.208–0.630)	0.990 (0.987–0.994)

PPV=positive predictive value; NPV=negative predictive value; MCI=mild cognitive impairment; AD=Alzheimer's disease; DLB=dementia with Lewy bodies; bvFTD=behavior variant fronto-temporal disease.

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