Chapter 7
Preliminary diagnosis of cognitive decline

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Key points

- The clinical diagnosis of dementia is usually determined in the primary healthcare setting.
- An investigation is subsequently conducted to determine the cause of dementia.
- At the primary level, treatable causes of cognitive decline should be identified.
- Specialised assessment and advanced biomarker studies should be conducted in individuals with atypical, early-onset and rapidly progressive dementias.

This is a chapter of the *World Alzheimer Report 2021, Journey to a Diagnosis of Dementia* which can be accessed in full at: https://www.alzint.org/resource/world-alzheimer-report-2021/

General background

The diagnostic process is a journey, and it starts at the first medical appointment where the primary goal is to summarise the progression of the person's memory and thinking problems, from the beginning to present-day. This consists of having the individual experiencing forgetfulness and a knowledgeable informant (carer, family member or friend) relate their experiences and observations about changes in memory, thinking, and personality over the past few years. Through careful questioning, the consultation aims to identify what cognitive or behavioural problems the individual has undergone, when these changes were initially perceived and how they have declined since that time. The healthcare professional will then assess memory, thinking and mood using standardised questionnaires as well as conduct a physical examination. Supplementary questions are meant to ascertain any limitations their cognitive problems have imposed on their activities of daily living. This information will help to determine whether the person has dementia as well as orient and design an investigation plan to determine its cause. When necessary, the healthcare professional will request blood tests and a brain scan to exclude other treatable causes of cognitive decline. There are several scenarios to consider once the clinical assessments and laboratory tests are completed and reviewed. From a practical perspective, distinguishing between a typical case of a person with dementia from those who may benefit from additional assessment tests available in specialised centres is imperative.

Survey results

The 1,111 multidisciplinary clinicians who participated in the survey unanimously indicated that clinical history, cognitive testing, and a physical examination were all valued components of a routine clinical assessment to determine dementia. Despite 12% of diagnoses occurring in a single visit, given the multiple facets involved in the diagnostic process, most agreed that it takes more than one visit to diagnose dementia.

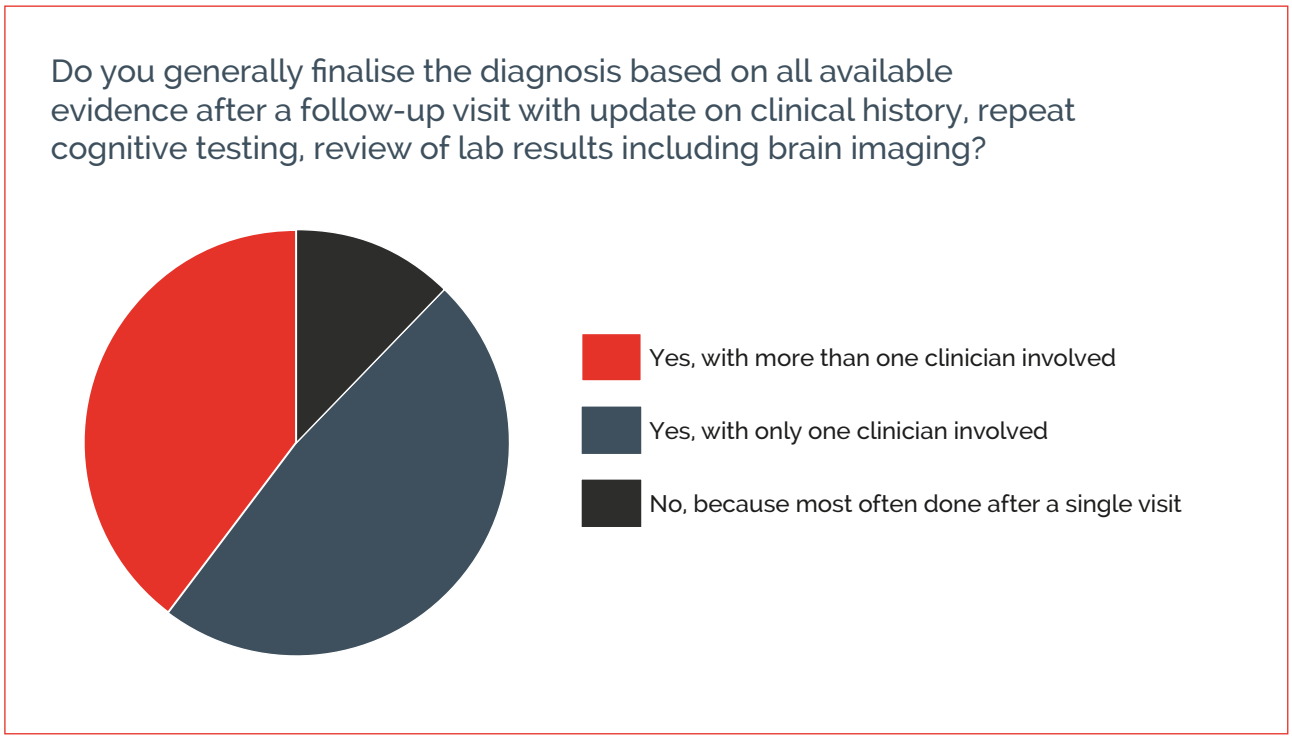

Chart 1. Clinician responses.

Medical history and clinical examination

As life expectancy around the world continues to rise, it is critical that clinicians become comfortable with the process of diagnosis, counselling, community and specialist referral, as well as pharmacological and non-pharmacological treatment options. Indeed, early diagnosis may allow for the identification of reversible causes, improved symptom management, and planning for the future. Cognitive decline may be part of normal ageing. Several genetic, socio-economic, cultural, and environmental factors contribute to a faster rate of age-related cognitive decline in healthy individuals. However, abnormal cognitive decline suggests the presence of a brain disease.

When a person presents with amnestic complaints, those characterised by an impairment to learn or recall new information, clinicians must consider differential diagnoses, among them dementia, delirium, depression, or psychosis. Comprehensive evaluations in specialised centres provide additional insight and corroborating evidence of a health concern or preliminary diagnosis. That is why people with atypical, young-onset and rapidly progressive symptoms benefit from these ancillary assessments. These centres have the expertise to guide the subsequent steps of the diagnostic journey in complex cases (1,2).

Past medical history should include learning disabilities, psychiatric disorders, alcohol or recreational drug abuse and risk factors of cerebrovascular disease. In addition to the routine review of systems, one should methodically investigate sleep abnormalities (hallucinations, sleep apnoea, somniloquy, patterns of movements or agitation), and endocrine. A complete drug history may reveal undesired interactions. Any family history of psychiatric and neurodegenerative conditions should also be systematically recorded. Finally, the clinical examination should include precise cardiovascular and neurological assessments.

Following a routine assessment (refer to Chapters 3–6), a preliminary diagnosis of an individual with cognitive complaints is based on the convergence of the information acquired. This inclusive and multidimensional perspective includes the (1) medical history (2) cognitive screening, (3)

functional assessments, (4) neuropsychiatric assessments, as well as the (5) physical examination. Collectively, data provide the basis for classifying whether the cognitive complaints the individual described are clinically significant, associated with mood changes and/or interfere with their daily activities.

Based on the results of the cognitive screening, a person may be considered cognitively unimpaired or impaired. Assessment of daily living activities, or functional skills, provides evidence of decline from a previous level of independence and autonomy in tasks such as managing finances, driving, participation in social and family activities, as well as household tasks.

Individuals with progressive cognitive complaints without deficits are characterised as having subjective cognitive decline. Individuals receive the diagnosis of mild cognitive impairment when their cognitive screening is abnormal, but their daily living activities remain unaltered or only minimally altered (3,4). People receive a dementia diagnosis when the screening tests indicating more than one cognitive abnormality are accompanied by a loss of independence or autonomy. It is important to emphasise that the diagnosis of mild cognitive impairment or dementia assumes that no other acute systemic or psychiatric condition that can explain the person's cognitive or functional abnormalities (1).

The determination of a person's dominant cognitive deficit, their respective age at onset and the rate of progression all provide the foundation to determine whether they have a typical or atypical presentation of cognitive decline. Typical dementia is characterised by slow and progressive cognitive decline with forgetfulness and difficulties retaining new information being the prevailing symptoms. This necessarily imposes significant limitations on an individual and highlights the uncertainty surrounding their ability to maintain their autonomy. Typical dementia is usually managed at the primary care level, as nearly 80% of people are diagnosed with Alzheimer's disease.

Atypical dementia designates those individuals where clinical presentation is dominated by non-memory deficits affecting language, behaviour, executive function, complex attention, perceptual-motor and social cognition. Early-onset dementia specifies those whose symptoms start before 65 years of age. Rapidly progressive dementia designates people whose decline within the MMSE parameters exceeds 3 points in 6 months. As a larger number of disease processes can cause atypical, early-onset or rapid progressive dementias, an accurate diagnosis is imperative for guiding families regarding prognosis. In summary, people with atypical, early-onset and rapidly progressive dementias require advanced diagnostic tests in specialised centres.

At the end of the preliminary assessment, healthcare professionals should indicate whether the patient has a normal cognition, mild cognitive impairment, a typical or an atypical dementia. The possible outcomes of the preliminary assessments are summarised in Table 1.

Table 1. Preliminary diagnosis of decline

Preliminary diagnosis	History				Basic assessments			Specialised assessments
	Age at onset	Clinical course	Dominant symptom	Psychiatric symptoms	Cognitive screening	Functional assessments	Clinical examination	
SCD		slow	memory	one or mild	normal	normal	normal	not necessary
MCI	65 +	slow	memory	none or mild	abnormal	minimal impact	normal	not necessary
Typical presentation	65 +	slow	memory	none or mild	abnormal	loss of autonomy	normal	not necessary
Atypical presentation	< 65	fast or stepwise	language behaviour executive function, complex attention, perceptual-motor, social cognition	none or mild or severe	normal/ abnormal	loss of autonomy	normal/ abnormal	recommended

Subsequent laboratorial evaluations to be conducted at primary care level

At the primary care level, it is important to rule out treatable causes of cognitive decline. These causes may include stroke, chronic subdural haematoma; meningitis, encephalitis, abscess; medication side effects or toxicity; vitamin B12, thiamine, or niacin deficiency; metabolic disorders such as hypothyroidism, hepatic encephalopathy, hypercalcemia, hyper- and hypoglycaemia, hyper- and hyponatremia. syphilis, HIV, accidental exposure to toxic substances, substance abuse, delirium; primary psychiatric conditions; or brain tumours. The frequency of treatable cases of cognitive decline might change depending on cultural, social economic and geographical circumstances (5).

Laboratory testing

A universal list of laboratory tests that can exclude reversible causes of dementia remains a matter of debate given the absence of studies conducted on a global level. The economic and medical impact of these tests is discussed in Chapter 12. Apart from a complete blood count, screening for vitamin B12 deficiency and hypothyroidism, additional tests such as screening for neurosyphilis and HIV should be ordered depending on the clinical history and specific cultural socioeconomic and geographic circumstances (refer to Chapter 8). The same reasoning is applicable for electrolytes, liver, kidney function panels as well as screening for hyperlipemia and diabetes (Chapter 8).

Neuroimaging

Structural neuroimaging obtained with either head Computed Tomography (CT) or Magnetic Resonance Imaging scans identify focal brain atrophies, the hallmark of neurodegenerative conditions. There is a consensus regarding the importance of CT or MRI scans at the primary care level for assessing people with possible cerebrovascular disease or atypical, rapidly progressive or early-onset dementia cases. However, neuroimaging for typical dementia assessments is not universally supported given its high cost and limited availability in certain low- and middle-income countries (refer to Chapter 9).

Specialised neuropsychological and speech assessments

After ruling out the presence of other diseases that may exacerbate dementia symptoms, it is plausible to request specialised care for patients with the atypical (non-amnestic) presentation of dementia, given the complexities associated with the diagnosis and management of these cases. The same is applicable for young-onset and rapid progressive cases. Dementia specialised centres or memory clinics have the expertise to guide the subsequent steps of the diagnosis journey in complex cases.

Specialised neuropsychological and speech assessments

Formal neuropsychological assessment testing is recommended to further characterise cognitive deficits in memory, language, behaviour, executive function, complex attention, perceptual-motor or social cognition. A complete neuropsychological assessment quantifies deficits not fully revealed by the routine cognitive screening tests. Speech-language assessments are relevant for detailing language deficits and speech abnormalities in people with primary progressive aphasia (6–8).

Specialised genetic assessments

There are a few scenarios where genetic assessments are required to corroborate a dementia diagnosis. In fact, numerous instances of dementia diagnosis within a family frequently prompts a cognitively impaired or unimpaired individual to seek a medical consultation. An autosomal dominant familial gene pattern justifies a genetic assessment. Another common situation may be that clinicians are asked to provide guidance regarding results obtained from direct-to-consumer genetic testing (9).

Biomarkers

Biomarkers are biological measures that detect the presence of a disease process causing dementias (10). These special biomarker laboratory tests can be obtained using Positron Emission Tomography (PET scans; Chapter 10), Single-photon Emission tomography (SPECT, Chapter 13), analysis of the cerebrospinal fluid (Chapter 11) and more recently, blood tests (Chapter 13). Biomarkers indicate the degenerative process present in the brain of people with dementia. In some countries, dementia biomarker tests have been approved for clinical use under specific Appropriate Use Criteria (AUC). In general, these clinically approved tests can identify the presence of amyloid plaques, neurofibrillary tangles, or dementia-related brain injury.

Conclusions

The clinical diagnosis of dementia is reached at the primary healthcare setting. It starts with medical history, questioning the person with dementia about symptoms, and the person accompanying them to the appointment about observed cognitive changes and conducting a physical examination. From there, the assessment may include screening for cognitive deficits, psychiatric symptoms and a function-focused approach regarding the extent of the individual's abilities to perform activities of daily living. A primary care clinician may request blood screening and neuroimaging to rule out treatable causes of cognitive decline.

While the vast majority of individuals will remain, and receive treatment, in the primary care setting, those who present with atypical dementia symptoms, early-onset or rapidly progressive dementias benefit from additional assessments in specialised centres. At the end of the preliminary assessment, healthcare professionals should indicate whether the person has a normal cognition, mild cognitive impairment, a typical or an atypical dementia.

In the prospects for upcoming disease-modifying interventions for dementia, biomarkers may become an important tool for primary care. Biomarker testing including PET, SPECT and even blood tests are significant indicators of the degenerative process occurring in the brain and clinical use of these tests at the primary care level for dementia diagnosis are promising for forthcoming therapies.

Additional references

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, 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. Alzheimer's Dement [Internet]. 2011 [cited 2021 Jul 8];7(3):263–9. https://pubmed.ncbi.nlm.nih.gov/21514250/
2. Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature [Internet]. 2018;554(7691):249–54. https://doi.org/10.1038/nature25456
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):270–9. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.008
4. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):280–92. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.003
5. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA – J Am Med Assoc [Internet]. 2019 Oct 22 [cited 2021 Jul 9];322(16):1589–99. https://pubmed.ncbi.nlm.nih.gov/31638686
6. Botha H, Josephs KA. Primary progressive aphasias and apraxia of speech. Contin Lifelong Learn Neurol. 2019;25(1):101–27.
7. Krein L, Jeon YH, Amberber AM, Fethney J. The Assessment of Language and Communication in Dementia: A Synthesis of Evidence. Am J Geriatr Psychiatry [Internet]. 2019;27(4):363–77. https://dx.doi.org/10.1016/j.jagp.2018.11.009
8. Warren JD, Warrington EK. Chapter 14 Cognitive Neuropsychology of Dementia Syndromes. Vol. 30, Blue Books of Neurology. ; p. 329-80: Elsevier; 2007. 329–380 p.
9. Koriath CAM, Kenny J, Ryan NS, Rohrer JD, Schott JM, Houlden H, et al. Genetic testing in dementia – utility and clinical strategies. Nat Rev Neurol [Internet]. 2021;17(1):23–36. https://dx.doi.org/10.1038/s41582-020-00416-1
10. Hansson O. Biomarkers for neurodegenerative diseases [Internet]. Vol. 27, Nature Medicine. Nature Publishing Group; 2021 [cited 2021 Jul 12]. p. 954–63. https://www.nature.com/articles/s41591-021-01382-x.