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SIN DOCUMENT

The Dementia Study Group of the Italian Neurological Society*

Guidelines for the diagnosis of dementia and Alzheimer's disease

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Introduction

These guidelines were prepared by the Dementia Study Group of the Italian Neurological Society (SIN) with the aim of defining criteria for the diagnosis of dementias and Alzheimer's disease. Their purpose is to describe a uniform diagnostic approach that makes it possible to identify the type and severity of cognitive and functional impairment, distinguish the various forms of dementia, and construct the premises for a correct prognostic evaluation. Further objectives of these guidelines are to encourage standard levels of care, promote collaborative research into areas of uncertainty, and define the quality characteristics distinguishing Dementia Referral Centres.

The recommendations contained in this document are designed for neurologists and other specialists involved in the complex process of diagnosis, as well as for general practitioners who observe the first signs and symptoms of dementia. The indications may also be useful in defining the resources necessary for the care of demented subjects. These guidelines may not be appropriate in all cases and should therefore be adopted only after having carefully evaluated the specific characteristics of each patient.

The guidelines are based on the scientific evidence emerging from a critical reading of articles published in peer-reviewed journals. Only in the case that the published findings were found to be insufficient or contradictory did we rely on the professional judgement and opinions of the members of the Study Group.

We started by critically reviewing the existing guidelines that have confronted the problem of diagnosing dementia, and by referring to original scientific articles whenever the current recommendations and guidelines were unsatisfactory or insufficient in terms of methodology or the conclusions reached.

The strength of every statement or recommendation contained in the present guidelines has been classified as follows:

I. Completely supported by scientific evidence
II. Supported by single-case, incomplete or contradictory scientific evidence
III. Based on the consensus of the experts preparing the guidelines

Each statement or paragraph of the guidelines is followed by a roman numeral (I, II or III) that indicates its strength. For the preparation of this report, the Study Group examined the following published guidelines:

- Early identification of Alzheimer disease and related dementias. Clinical practice guideline, 1996 [1].
- Fairhill guidelines on ethics of the care of people with Alzheimer's disease: a clinical summary. American Geriatrics Society, 1995 [2].
- Statement on use of the apolipoprotein E testing for Alzheimer's disease. Consensus statement of ACMG: ASHG, 1995 [3].
- The clinical introduction of genetics testing for Alzheimer's disease. National Institute of Health – Centre for Biomedical Ethics, 1997 [4].
- Canadian guidelines for the development of antidementia therapies. A conceptual summary. Consortium of Canadian Centres for Clinical Cognitive Research, 1995 [5].
- Practice guidelines for the treatment of patients with Alzheimer's disease and other dementias of late life. American Psychiatric Association Work Group on Alzheimer's Disease and Related Dementias, 1997 [6].
- Screening for dementia. Guide to clinical preventive services. US Preventive Services Task Force, 1996 [7].
- Malattia di Alzheimer. Documento di consenso. Società Italiana di Neuroscienze, 1999 [8].

Our guidelines reflect the state-of-the-art and the convictions of experts at the time they were drawn up. The orientation and substance of the recommendations may be modified in the future on the basis of new scientific findings and the results of the continuous process of validation that the SIN intends to establish by means of its Dementia Study Group. In the case of still controversial subjects or issues that are not sufficiently documented scientifically, we have indicated the need for further studies.

The present guidelines offer a response to a number of questions judged to be of fundamental importance for correct patient management:

- Diagnostic criteria
- Early diagnosis
- Diagnostic pathways and the role of general practitioners and neurologists
- Main objectives of the diagnostic work-up
- Differential diagnosis

Diagnosis

Dementia is characterised by the presence of a memory deficit associated with disturbances in other cognitive areas that causes a significant reduction in the everyday life abilities of the patient. The diagnosis should be based on the DSM-IV or ICD-10 criteria that assume the existence of a single syndromic picture (dementia) common to various diseases (III).

However, the DSM-IV and ICD-10 diagnostic criteria leave some open questions that are still subjects of research and sources of uncertainty. These include the differentiation of normal cerebral aging and dementia, the nosological definition of cases reflecting the isolated impairment of only one cognitive ability, and the diagnostic role of the behavioural disturbances that often (if not invariably) characterise demented patients (III).

The diagnosis of dementia is prevalently clinical. In the case of Alzheimer's disease (the most frequent of all of the forms of dementia) and all of the other forms that are not clearly hereditary, there are still no biological or instrumental markers that can be definitively used for diagnostic purposes (I).

The identification of biological and instrumental disease markers is a priority objective that must be pursued within the ambit of specific research protocols (III).

Early diagnosis

Although there is evidence that the initial phases of dementia are often not recognised [9, 10], an early diagnosis would allow:

- Timely intervention against the causes of reversible dementias
- Initiation of therapies that may delay the progression of the disease
- Initiation of therapies that may potentiate cognitive performance by taking advantage of the fact that neuronal circuits are still partially functioning
- Adoption of measures that reduce the effects of dementia-related comorbidities
- Timely implementation by patients and their families of the measures necessary to solve the problems related to the progression of the disease (III).

Some screening instruments can reveal cognitive or functional deficits in asymptomatic subjects, and may significantly shorten the time of diagnosis. However, their specificity is unsatisfactory and, if they were to be used in populations of asymptomatic subjects, there would be a large number of false-positive results [11] (I).

It is therefore inadvisable to use the existing instruments for screening asymptomatic populations insofar as they do not offer any public health advantages (I).

However, investigations of this type are of great scientific interest and should therefore be pursued within the context of specific research protocols that explicitly foresee the participation of a specialised neurologist (III).

Given the advantages of an early diagnosis, dementia should be immediately suspected in the case of elderly sub-

jects who show an initial decline in cognitive capacity. The prevalence of dementia in the elderly is higher than in asymptomatic subjects, and the use of screening instruments has a greater positive predictive value and is less likely to lead to false-positive results. A prompt diagnosis in subjects with initial symptoms is here called a "timely diagnosis" in order to distinguish it from an early diagnosis made during the asymptomatic phase (I).

The symptoms that frequently characterise the onset of dementia and indicate the need to begin a search using a screening test can be described [1]. A subject may show progressive difficulty in performing one or more of the following:

- *Learning and remembering new information.* The patient is more repetitive, has difficulty remembering recent conversations, events and appointments, and frequently positions objects badly.
- *Doing complex tasks.* The patient has difficulty following a complex series of thoughts or doing tasks that require a large number of actions.
- *Reasoning.* The patient is incapable of suggesting a reasonable strategy for solving problems at home or work, and/or strangely fails to respect the rules of social behaviour.
- *Self orientation.* The patient has orientation difficulties when driving and tends to get lost in previously familiar places. The patient may find it difficult to remember the current date or day of the week.
- *Speaking.* The patient has increasing difficulty following conversations and finding the words that express what he wants to say.
- *Adopting adequate behaviours.* The patient is passive, inadequately reacts to different situations, is more irritable and suspicious than usual, and wrongly interprets auditory and visual stimuli.

Subjects with dementia sometimes manifest other more selective and particular disturbances affecting language (aphasia), the ability to recognise familiar faces (prosopoagnosia) or the capacity to organise movements.

Diagnostic work-up

In addition to gathering the relevant anamnestic data and considering the results of a physical examination, the diagnostic work-up should also include a careful evaluation of the patient's functional and cognitive abilities [12]. This requires the involvement of general practitioners in the first screening phase and specialised neurologists in subsequent phases of diagnostic confirmation and differential diagnosis (III).

Dementia is the impairment of memory and at least one other cognitive ability, accompanied a reduced functional capacity. In the case of some forms of dementia other than Alzheimer's disease, the appearance of a memory disorder may be preceded by major behavioural disturbances. It is also not infrequent to observe patients with an isolated deficit of memory or another cognitive function, or with impaired memory and other cognitive functions but without any reduction in functional capacities. These pictures should unequivocally be described using terms such as "isolated impairment of memory, orientation or language…" or "mild cognitive impairment" in the case that a functional deficit is not present. These patients should be carefully evaluated at the time of diagnosis and during the course of follow-up by means of specific protocols (Table 1) (III).

Phase 1. Screening

Screening, which can prevalently be managed by general practitioners, has the aim of:

- Formulating a diagnostic hypothesis
- Identifying possible causes of the cognitive deficit

Directed anamnesis. Careful attention should be paid to the possible presence of serious internal diseases that may give rise to encephalopathy, such as hyper- or hypothyroidism, renal, hepatic or respiratory insufficiency, diabetes or arterial hypertension (I). Consideration should also be given to conditions that can cause a deficiency in folic acid or vitamin B12, both of which are known to cause or contribute to the manifestation of reduced cognitive capacity (I).

It is necessary to evaluate the possibility of alcohol or other substance abuse, and of the exposure to toxins in the home or work environment. The presence of psychiatric diseases, previous cranial traumas and, in particular, other neurological diseases should also be investigated (I).

Particular attention should be given to the drugs being taken by the patient insofar as many of these may mimic the presence of, or aggravate, dementia, especially in the elderly. These syndromes can easily be controlled or improved by discontinuing or reducing the dose of the drug involved (I). It is also essential to investigate whether there is a family history of dementia (I).

Directed physical examination. The physical examination must take into account general medical principles and necessarily include a complete neurological examination (I). Careful attention should be given to the possibility of any physical or sensory impairments that may explain abnormal test results (I).

Functional evaluation. This evaluation can be made informally by asking the subject and his relatives how he manages the activities of everyday life. Each physician should become familiar with at least one standardised scale of such activities. The instrumental activities of daily living (IADL) scale is recommended; this investigates eight activities and is often used during the course of controlled clinical studies [12] (I).

Table 1 Diagnostic investigations performed in the case of suspected dementia

Examination	Advice	Comments
Directed anamnesis	Indicated	A precise search for disturbances affecting memory, language, attention, judgement, space/time orientation, etc.
General physical and neurological examination	Indicated	A precise search for signs of systemic and/or neurological disease (focal, extrapyramidal, etc.)
Neuropsychological evaluation		Identification of cognitive deficit
Screening battery	Indicated	Definition of the cognitive profile and the severity
Complete battery	Indicated	of the deterioration
Specific tests	Special	Definition and quantification of the deficit affecting specific cognitive areas
Laboratory tests		
Blood and urine tests	Indicated	Exclusion of significant systemic diseases or identification of vascular risk factors
Serum syphilitic tests	Indicated	Syphilitic dementia
Vitamin B12, folic acid	Indicated	Exclusion of vitamin deficiency
Thyroid function	Indicated	Exclusion of thyroid dysfunction
HIV	Special	In subjects with cognitive impairment of unknown origin, particularly if young
Screening for metabolic diseases	Special	Wilson's disease, mitochondrial diseases, etc.
Genetic investigations	Special	Forms of Alzheimer's disease of autosomal dominant inheritance Huntington's disease
Chest X-ray	Indicated	Exclusion of chronic obstructive respiratory diseases
Electroencephalography	Indicated	Particular forms of encephalitis and Creutzfeldt-Jakob disease
Cranial CT or MRI	Indicated	Exclusion of structural lesions (hydro-cephalus, subdural haematoma, intracranial tumours); identification of cortical and/or subcortical atrophy or temporal lobe atrophy in the early phases of Alzheimer's disease
SPECT or PET	Supplementary	Identification of functional deficits in morphologically undamaged areas
CSF examination	Special	Useful in the case of suspected vasculitis or infective or inflammatory diseases of the CNS

Indicated, tests or examinations indicated in the majority of cases of suspected dementia; *Special*, tests or examinations that may be useful in particular cases; *Supplementary*, examinations offering complementary information; *HIV*, human immunodeficiency virus; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *SPECT*, single photon emission computed tomography; *PET*, positron emission tomography; *CSF*, cerebrospinal fluid; *CNS*, central nervous system

Cognitive evaluation. In the initial phases of dementia the very presence of deterioration may be uncertain. A systematic investigation of the different cognitive areas should always be undertaken. It is also preferable for general practitioners to do a formal investigation using standardised, structured instruments. The aims of this study should be to obtain objective indications concerning the existence of a cognitive deficit, identify the affected areas, and quantitatively evaluate its severity. This information may be useful during the follow-up (III).

A large number of screening instruments are available for investigating the different cognitive areas. The most widely used is Folstein's mini-mental state examination (MMSE), the Italian version of which has been validated in a population of normal Italians [13]. Another instrument validated for the Italian population is the Milan overall dementia assessment, which was constructed using the paradigm of Alzheimer's disease [14].

Screening tests alone do not permit a diagnosis of dementia, although they can quantify the level of individual cognitive deficit. Nevertheless, they can document the presence of reduced cognitive function in multiple domains, as required by the diagnostic criteria of dementia (I).

Laboratory tests. Although the details depend on the suspected diagnosis, the following laboratory tests can be considered necessary and should be routinely carried out:

- Haemochrome with formula
- Electrolytes

- Erythrocyte sedimentation rate (ESR)
- Glycaemia
- Azotaemia
- Creatininaemia
- Urine composition
- Thyroid function (to exclude dementia due to hypo- or hyperthyroidism)
- Blood vitamin B12 and folate levels (to exclude dementia due to vitamin deficiency)
- Syphilis serology (to exclude luetic dementia).

Other laboratory tests may be useful in individual patients, although they do not need to be carried out routinely:

- Hepatic function
- Serology for HIV-1 (AIDS-dementia complex)
- Chest X-ray and blood gas analysis (chronic hypoxy syndromes)
- Urinary metabolites of drugs of abuse
- Urinary excretion of heavy metals
- Auto-antibody titre for the presence of auto-immune diseases.

Phase 2. Diagnostic confirmation and differential diagnosis

Cerebral neuroimaging. Brain neuroimaging examinations should be considered on the basis of the clinical characteristics at presentation. However, it is reasonable to perform brain computed tomography (CT) or magnetic resonance imaging (MRI) at least at the time of first diagnosis, because this is often indispensable for a correct differential diagnosis (I).

Other examinations, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), can provide information on brain function. These are of great interest for research purposes and should be used in the framework of research protocols (III).

Neuropsychological evaluation. Although not strictly necessary for diagnosing dementia, at the time of first diagnosis (and particularly in the case of Alzheimer's disease), each patient should undergo a complete neuropsychological evaluation (II).

An adequate neuropsychological test battery can provide indispensable indications of the existence and severity of cognitive deficit and the impaired cognitive areas, and can help in evaluating disease progression during follow-up. To this end, the use of batteries validated in Italian populations is recommended, such as the mental deterioration battery (MDB) [15] or the battery proposed by the Italian Muticentre Study of Dementia (SMID) [16] (II).

Alongside the use of standardised neuropsychological test batteries, the patient's cognitive status should be further explored using tests that investigate particular functional areas (III).

Behavioural and psychiatric evaluation. The presence of behavioural disturbances should be at least informally investigated in all subjects (II). Depression should be evaluated with particular care, preferably using standardised instruments such as Hamilton's scale or Beck's inventory, as it can affect cognitive performance or be a reactive response to the cognitive disturbance itself (I).

The use of instruments for the quantitative evaluation of behavioural disturbances is recommended. One of the most widely used is the neuropsychiatric inventory (NPI), of which an Italian version exists [17, 18] (III).

CSF examination. A lumbar puncture should be performed in the presence of known or suspected meningeal carcinomatosis, central nervous system infection, positive syphilitic serology, suspected central nervous system vasculitis, unusual or rapidly progressive dementia, or immunosuppression (I).

The cerebrospinal fluid (CSF) levels of substances that may play a pathogenetic role in dementia (e.g. beta-amyloid, tau protein) are of great scientific interest. These should be measured in the context of research protocols which explicitly require that informed consent be obtained from the patient or caregiver [19] (III).

Electroencephalography. Electroencephalography is fundamental when evaluating suspected encephalitis or Jakob-Creutzfeldt's disease or in the presence of epileptic seizures (I).

Differential diagnosis

The primary objective of differential diagnosis is to identify the dementias that may regress or not progress once the causes have been removed (I). Among the various clinical forms, one of the most difficult to distinguish from degenerative dementias is "depressive pseudodementia". In this case, the distinction is often facilitated by means of careful neuropsychological examinations repeated over time and after any specific therapy (II).

Once having excluded the possibility that the dementia is due to removable causes, it is necessary to identify the dementias of vascular origin. In this case, it is reasonable to expect that controlling vascular risk factors will reduce the frequency of the recurrence of vascular episodes and improve the prognosis (II).

Having also excluded the presence of vascular dementia, we are in the presence of a primary degenerative dementia. Although the most frequent and paradigmatic of these is Alzheimer's disease, it is becoming increasingly possible to recognise a certain number of diseases and syndromes which, although falling within the general picture of dementia, have particular characteristics in terms of their hereditary nature,

clinical manifestations and, above all, treatment response (I).

Furthermore, classification of the different manifestations and syndromes is a necessary premise for being able to identify more easily in the future those forms that respond to different treatments and the etiopathogenetic mechanisms of the diseases [20] (III).

Classification of the dementias

Treatable dementias

These are generally attributable to infective, metabolic or psychiatric causes, space-occupying lesions or normotensive hydrocephalus, and account for less than 15% of all dementias. They can be recognised using the clinical, laboratory and instrumental examinations previously described.

Normotensive hydrocephalus is characterised by gait disturbances, urinary incontinence and cognitive decline, which usually appear in this order. It may sometimes respond to ventriculoperitoneal shunting (I).

Once these conditions are excluded, the most frequent dementias are Alzheimer's disease and vascular dementias.

Vascular dementias

These make up about 10%-15% of all dementias and are caused by one or more small or large infarctions. Criteria have been proposed for the diagnosis of probable vascular dementia [13], which can be formulated on the basis of:

- Clinical evidence of dementia
- Clinical and neuroimaging (CT, MRI) evidence of cerebrovascular disease
- Evident or indirect relationship between the dementia and the cerebrovascular disease (e.g. onset, fluctuations, "stepped" deterioration in cognitive deficits).

Having reached a diagnosis of vascular dementia, it is useful to differentiate the following subtypes:

- *Multi-infarctual dementia (MID).* This is the result of multiple and complete infarctions generally in the cortical and subcortical territory of the great vessels (II).
- *Dementia due to individual strategic infarctions* arises as a result of single infarctions in cerebral areas (e.g. gyrus angularis, basal proencephalon, thalamus) that are functionally important for cognitive performances (II).
- *Small vessel dementia.* This is the result of ischaemic lesions of the small vessels that feed the subcortical structures (II).
- *Dementia due to hypoperfusion.* This is the result of acute, chronic or repeated hypoxic damage (II).
- *Haemorrhagic dementia.* This is the sequela of intraparenchymal (among the most frequent forms of intracerebral capsular haemorrhage) or extraparenchymal (chronic subdural haematoma, subarachnoid haemorrhage) haemorrhagic lesions (II).

Primary degenerative dementias

Having excluded the possibility of vascular dementia, it is necessary to make a further differential diagnosis among the remaining non-secondary degenerative dementias. One possible classification identifies the following forms of dementia [21] (III).

Alzheimer's disease. The most widely used criteria for the diagnosis of Alzheimer's disease are those proposed in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association Work Group (NINCDS-ADRDA) and DSM-IV. The NINCDS-ADRDA criteria foresee different levels of diagnostic probability. The clinical diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA and DSM-III R criteria (almost identical to those of DSM-IV) is confirmed by neuropathological diagnosis in 89%-100% of cases [22, 23] (I).

In cases in which familial investigations reveal a dominant autosomal transmission, a genetic examination is indicated with the aim of identifying amyloid precursor protein (APP) or preseniline 1 and 2 (PS1 and PS2) gene mutations (I). Other genetic investigations of factors potentially capable of modulating the clinical characteristics of the disease (e.g. ApoE, IL-1α) are of great scientific interest. These should be performed within the context of specific research protocols (III).

Neurofibrillary tangles (NFTs) with neuritic plaques and dystrophic neurites are considered to be the most distinctive signs of Alzheimer's disease, even though the disease has considerable clinical, genetic and neuropathological heterogeneity. However, the concomitance of dementia and Alzheimer-type neuropathological lesions in patients with Parkinson's disease and Lewy body dementia suggests that these different clinical forms probably have a common pathogenetic mechanism [24]. There is still no unanimous consensus concerning the definition of the neuropathological criteria typical of Alzheimer's dementia [25, 26]. The diagnosis is based on autoptic findings of senile plaques, neurofibrillary deposits and amyloid angiopathy, which represent typical but not exclusive disease markers. The neuropathological markers of Alzheimer's disease can also be found in undemented elderly subjects. The anatomopathological finding of Alzheimer's disease is useful confirmation in the case of clinically diagnosed dementia (I).

Frontotemporal dementia including Pick's dementia. This group of dementias, indistinguishable from Alzheimer's disease during intermediate and late stages, is initially characterised by

the predominance of behavioural, affective and language symptoms over a mild or even absent memory deficit (II).

Creutzfeldt-Jakob and other prion-induced diseases. Although extremely rare, these dementias need to be recognised because there is a risk of transmission following exposure to contaminated tissues as in the case of corneal transplants (I).

Dementia with Lewy bodies. This form is particularly frequent and may be the second most common form after the vascular dementias. From its earliest stages, it is accompanied by parkinsonian signs (bradykinesia and rigidity, although tremor at rest is rarely present). The cognitive signs, which normally precede the motor signs, often take the form of a slowing in thought and action (bradyphrenia, psychomotor slowing). In comparison with Alzheimer's disease, the cognitive deficits (particularly vigilance and attention) tend to be more fluctuating but the disease has a more rapid course. Given that parkinsonian signs appear late or not at all in patients with classic Alzheimer's disease, dementia with Lewy bodies must always be suspected in Alzheimer patients showing early extrapyramidal signs. In addition to motor signs, this dementia is also characterised by the frequent and even early presence of particularly visual hallucinatory symptoms, which are precisely detailed and reiterated [27] (II).

Despite the relatively low specificity of these symptoms and signs for the purposes of differential diagnosis, it is important to be able to arrive at a grounded suspicion of Lewy body dementia because the affected patients are particularly sensitive to neuroleptics (III).

Parkinson's disease. Dementia is a frequent complication of advanced Parkinson's disease (I).

Progressive supranuclear paralysis. Dementia complicates 70%-80% of the cases of this parkinsonian syndrome, which is predominantly characterised from the beginning by symptoms involving combined eye movements. In particular, the characteristic sign of a vertical glance disturbance is often present from symptom onset (I).

Basal cortical degeneration. This is an increasingly diagnosed cause of Parkinson's disease with dementia. Unlike in the case of Lewis body dementia, the often unilateral motor signs precede the dementia, and ideative and ideamotor apraxia appears even years before the development of global cognitive deficit (II).

Huntington's disease. This is an autosomal dominant hereditary disease. The clinical signs of involuntary movements (chorea) and psychiatric symptoms appear before the onset of dementia. In addition to identifying a positive family history, it is now possible to make a genetic diagnosis (II).

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