Depression, Dementia, and Pseudodementia

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Abstract

Depression and dementia represent frequent clinical presentations in the elderly population. Both diseases are interlinked. Indeed, depression in the elderly may reflect an increased risk for the later development of dementia. Worldwide, about 47 million people are affected by dementia, which represents about 10% of the general population over 65 years of age. On the other hand, among elderly people, the prevalence of depressive symptoms and major depressive disorder (MDD) is 15% and 1–3%, respectively. Female gender, alcohol and substance or drug abuse, family history, and medical conditions are factors associated with depression in the elderly.

In the present chapter we specifically focus on discrimination between elderly MDD and major neurocognitive disorder. Concerning this point, two steps have to be performed: (1) observation of clinical response to antidepressants' treatment, taking into consideration a possible longer latency of antidepressants' efficacy in elderly/lower response to antidepressants in older age, and (2) cross-clinical assessments with neuropsychological evaluation, imaging, and laboratory tests.

Considering the background of the present literature, we pointed out the case of a woman, 72 years old, with a long history of MDD and a recent diagnosis of mild cognitive impairment (MCI). She was referred to our outpatient clinic for a relapsing depressive episode. In the present case presentation, we investigated the differential diagnostic process, observing clinical course, using neuropsychological evaluation, blood and urine laboratory exams, computed tomography, magnetic resonance imaging, positron emission tomography, cerebrospinal fluid analysis, and electroencephalogram.

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10.1 Introduction

Depression and dementia are frequent in the elderly [1] and seem not to be completely independent: many studies have shown how history of elderly depression may increase risk for later development of dementia [2, 3]. Therefore assessing late-life depression could be relevant in relation to possible onset of dementia [4].

Some epidemiological studies have shown that in about 15 years the elderly population is expected to reach 20% of the general population [5], with an increase of specific health problems, including depression and progressive cognitive deficits.

10.1.1 Epidemiology

Worldwide about 47 million people are affected by dementia, with nearly 9.9 million new cases per year [6], which represent about 10% of the general population over 65 years of age [7]. Both incidence and prevalence increase with older age [8]. The most frequent kind of dementia is Alzheimer's disease (42%), followed by vascular dementia (26%), mixed dementia (caused by both Alzheimer's and vascular disease—12%), frontotemporal dementia (FTD—9%), Lewy body dementia (8%), and Creutzfeldt-Jakob's disease (3%) [9].

75% of people suffering from Alzheimer are affected by a sporadic form of Alzheimer's disease with a late onset, the remaining 25% by a familial one, which is due to genetic factors and is characterized by earlier onset (around 55 years). Vascular dementia characterizes elderly population with cardiovascular risk factors such as hypertension, heart disease, hypercholesterolemia, and thrombosis [9].

Frontotemporal dementia has the earliest onset: it usually peaks at 58 years of age, although large variability is possible, with cases where it arises in the second or in the ninth decade of life [10, 11].

On the other hand, mood disorders are widespread: it has been estimated that 1/7 of the general population is affected over the whole lifetime [12]. Among elderly people, the prevalence of depressive symptoms and major depressive disorder (MDD) is 15% and 1–3%, respectively [13]. Female gender, alcohol and substance or drug abuse, family history, and medical conditions are factors associated with depression in the elderly. British and American studies reported a prevalence of a depressive clinical presentation in 14.7% to 20% of elderly people, whereas in the Canadian community, depressive symptoms are prevalent in 10% to 15% of the elderly population [14]; finally, European epidemiological data shows that, in

subjects aged 65 years, prevalence of depressive diagnoses ranges from 9% to 24%, with a mean value of 12% [15].

10.1.2 Diagnosis of Dementia

Global clinical examination is essential to recognize whether patients' symptoms and signs could be ascribed to a degenerative cognitive impairment and, more precisely, to dementia. A wide range of diagnostic tools, i.e., psychiatric, neurologic, and medical assessments, as well as blood and cerebrospinal fluid (CSF) and imaging studies, should be performed [16, 17]. Detailed anamnestic interview should be performed as a first approach to investigate psychiatric and/or neurological history, previous/ongoing medical conditions, and pharmacological history. The help of the patient's relatives or caregivers could be useful for clinicians [18]. Anamnestic results should be compatible with the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth version (DSM-5) [19], where the term "dementia," previously reported in the DSM-IV [20], has been redefined as "major neurocognitive disorder." To make a diagnosis, a significant cognitive decline from a previous level of performance should be investigated. Moreover, assessment of one or more cognitive domains (memory, language, executive functions, complex attention, perceptual-motor abilities, and social cognition) should be performed. Furthermore, cognitive deficits should interfere with one's independence in daily activities, and assistance should be required with complex instrumental daily living activities, such as paying bills or managing medications. Cognitive deficits should not occur exclusively in the context of a delirium and cannot be better explained by another mental disorder (e.g., MDD, schizophrenia).

After an accurate clinical assessment, impairment in cognitive performance has to be documented by standardized global functioning rating scale and neuropsychological testing, for example, IADL (instrumental activities of daily living) [21, 22], which investigates eight daily life activities. Other tests, such as Mini-Mental State Examination (MMSE) [23, 24] or the Mental Deterioration Battery (MDB) [25], can measure global cognitive performance and can be used as screening tests. Furthermore, blood and urine exams should be performed as soon as possible, both in hospitalized and in outpatients, to determine whether hydro-electrolyte alterations, thyroid dysfunction, or any infections have occurred. These medical conditions can be responsible for a delirium, which is characterized by confusion, loss of orientation, and memory impairment. In addition, plasma levels of daily medications should be monitored, because many psychiatric and nonpsychiatric drugs may cause hydro-electrolyte alterations or imitate symptoms or signs of the dementia spectrum when plasma levels are over the standard range [20].

Neuroimaging exams should be also taken into consideration. In particular, as a first step, a computed tomography (CT) is useful to exclude acute neurological conditions, such as stroke and intracranial hemorrhage. After that, magnetic resonance imaging (MRI) could show possible vascular neurodegeneration. Also positron emission tomography (PET), in addition to the previously listed imaging exams,

may help clinicians in the diagnostic processes of dementia [26]. The cerebrospinal fluid (CSF) examination can confirm the clinical and/or imaging suspect of dementia, and it could point to different forms of dementia [27, 28]. Lastly, the electroencephalogram (EEG) is considered a diagnostic completion exam which is able to exclude epileptic syndromes in elderly patients and can help to discriminate between healthy elderly subjects, Alzheimer's disease, and vascular dementia [29].

Box 10.1 Diagnosis of Dementia

- The presence of a significant cognitive decline from a previous level of performance.
- The domains concerned are complex attention, executive function, learning and memory, language, and social cognition.
- All this must be documented by standardized neuropsychological tests (IADL, MMSE, MDB).
- Cognitive deficits interfere with autonomy in daily activities.
- Patients must not be tested in the context of a delirium or other mental disturbance, in order to be able to provide a primary diagnosis.
- To differentiate the etiologic subtypes, additional diagnostic markers, in particular neuroimaging studies such as magnetic resonance imaging or positron emission tomography, may come into play.

10.1.3 Differential Diagnosis of Depression and Dementia

Geriatric pathologies are often characterized by an acute change in mental status, a clinical condition called delirium, which could be due to thyroid dysfunction, B12 vitamin deficiency, hydro-electrolyte alterations, and epileptic or vascular syndrome. This represents a possible confusing condition; nevertheless, differently from dementia, whose course is more progressive, delirium is characterized by an acute and reversible change in mental status, and this relevant feature allows the differential diagnosis.

However, discriminating between elderly major depression and major neurocognitive disorder is not easy. Concerning this point, it might be useful to perform the following steps [19]:

- Observation of clinical response to antidepressant treatment, taking into consideration a possible longer latency of antidepressant efficacy in elderly/lower response to antidepressants in older age [30]
- Cross-clinical assessments with imaging and laboratory tests

Box 10.2 Differential Diagnosis Between Depression and Dementia

Depression	*Dementia*
• Onset can be accurately datable	• Onset cannot be precisely dated
• Symptoms, often, are acute and progress quickly	• Onset is sneaky with subtle symptoms
• Frequently there is a positive psychiatric history	• Symptom progression is very slow
• Patients express strong discomfort and complain of the loss of cognitive efficiency, highlighting mistakes and engaging in little simple tasks	• Typically negative psychiatric history
• Affectivity is altered; there is loss of social-relational abilities	• Patients complain little about cognitive disorders but tend to hide their shortfalls
• Cognitive disorders do not worsen overnight	• Affectivity is evanescent with emotional disinhibition
• Attention and concentration remain preserved	• Social skills are conserved normally
• Subjects often answer "I don't know" to questions asked	• Frequently, symptoms worsen late in the afternoon or early evening
• Memory loss for both recent and past events	• Compromised memory and attention
• Sleep disorders	• The answers are often imprecise
• Frequent vegetative symptoms	• In orientation tests, patients confuse familiar and unknown things
• High risk of suicide	• Severe memory loss for recent events (anterograde memory)
	• Fatigue without drowsiness but with restlessness or stiffness or cramps
	• Absence of vegetative symptoms
	• Lower risk of suicide

10.2 Case Presentation

10.2.1 Clinical History and Presentation

Ms. S.C., 72 years old, was referred to our outpatient clinic for a relapsing depressive episode. She had a long history of major depressive disorder (MDD) and a family history of depression (mother). She was treated for hypertension, but did not have other diseases.

The patient has been known to the psychiatric services since 1973, when, aged 28, she was admitted to the psychiatric ward for the first time. On that occasion she presented symptoms of a major depressive episode (MDE) and was treated with non-referred antidepressants. The treatment resulted in full recovery and she did not receive neither maintenance treatment nor psychotherapy. After this episode, she described a few years of well-being. She relapsed three times from 1999 to 2007, each one following a stressful life event (e.g., divorce, economic collapse, second marriage). Every time, she fully recovered and interrupted the pharmacological treatment. The episodes were always treated in outpatient services and never became

so severe as to require admission to the psychiatric ward. From 2000 to 2007 the patient had a weekly session of cognitive psychotherapy.

In 2007, aged 62 years, her second husband died. After the mourning, depressive symptoms progressively worsened, and the patient contacted our psychiatric day hospital. During this episode, she referred slight memory loss. After a year and a half, neuropsychological tests resulted in range. Her mood worsened and she underwent two further hospitalizations in 2009 and 2010.

From 2010 to the present, the patient has been treated with several medicaments (antidepressants in association with atypical antipsychotics or mood stabilizers) and with psychological therapy. Mood deflection, hypersomnia, apathy, ablution, lack of initiative, and memory deficits remained rather constant.

Timeline of depression is reported in Fig. 10.1.

In January 2017, at the time of our first evaluation, the patient presented mood deflection, emotional liability, apathy, anhedonia, memory deficits, and reduction of daily functioning.

The patient had already been at our unit a few times in the previous 2 years. However, the day she came to our building, she got lost and went to the dentist's next door, believing that she was sent there to treat some teeth problems. She had a paper with the address, but was unable to reach the right place. She appeared confused and not oriented, so the dentist called our service to understand what was going on. She was then led to our service by a nurse and started to cry. She reported to have lost her keys several times in the last few months and to forget very simple daily tasks. She could not exactly refer her daily pharmacotherapy. She took 75 mg of clomipramine every day, in addition to random antidepressants. She reported that she helped herself to remember her daily medications by some notes she kept in the kitchen. Hamilton Depression (HAM-D) Rating Scale showed a mild-moderate depression (score = 18), with prevalent deficits of mood deflection and anhedonic and anxious sphere.

In day hospital she was treated with 50 mg of intravenous trazodone daily and 10 mg of vortioxetine daily. Her depressive symptoms partially decreased within 8 weeks and her HAM-D became 10. However, the patient remained sad, persistent in her speech, amnesic, and unable to cope with her daily activities. She seemed to have a global cognitive deficit.

10.2.2 Neuropsychological History and Previous Neuroimaging Results

The onset of the first symptoms of memory loss is 2007. The result of the neuropsychological evaluation was a "minimum cognitive deficit in amnesic-attentive capacities that appears to be consequent to an affective disorder rather than a primary

sign of neuro-progressive disease." A second evaluation performed in 2008 did not show cognitive deficits.

From 2009 to 2011, annual neuropsychological assessments revealed slight fluctuating deficits, defined as "minimal cognitive deficits consequent to anxiety and depression."

In 2012, the patient was diagnosed with *minimal cognitive impairment* (MCI), and the diagnosis was confirmed in the following 2 years.

The last neuropsychological evaluation was performed in 2014 and showed mild diffused cognitive deficits, with a worsening in speech tasks. Results have been ascribed to the patient's depressive disease.

Timeline of neuropsychological evaluation is shown in Fig. 10.2.

Neuropsychological tests have shown over time a decrease in tests that relate to selective attention, visual-spatial search capability, and memory. In this chart, we have reported the most important deficitary tests

In association with neuropsychological evaluations, the patient underwent several neuroimaging scans from 2007 to 2017.

In 2007 the brain RMN showed an expansion of the convexity liquor spaces, as well as micro-involutive lesions of the periventricular white matter (WM).

Another brain RMN carried out in 2014 confirmed the same result. In 2009 the brain SPECT resulted overall normal. In 2011 the brain RMN showed subcortical and periventricular WM point intensities, especially in the bilateral frontal lobes.

In February 2017 the patient underwent neuropsychological tests again, which showed "a multifocal cognitive decay." This condition was again considered secondary to a depressive disorder. However, the neuropsychological performance seemed to be more severe and spread to several other cognitive domains, so we

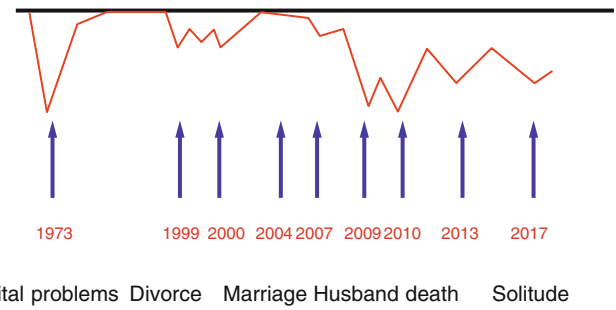


Fig. 10.1 Depression timeline

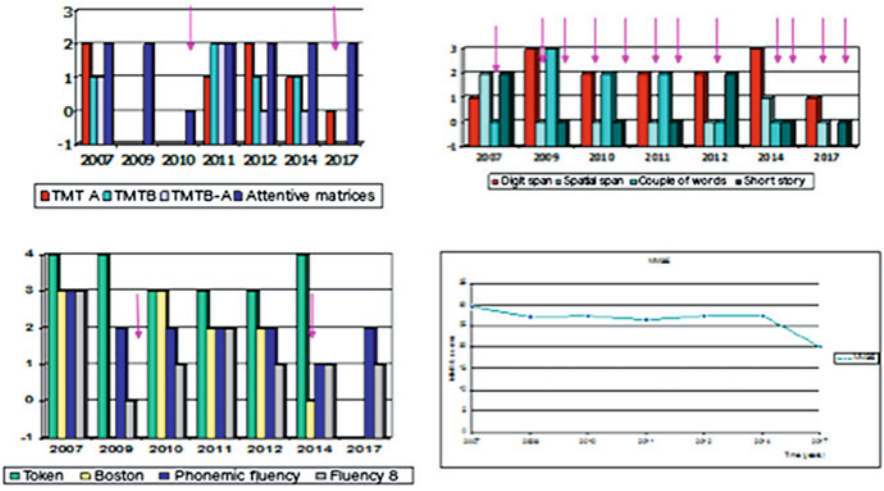


Fig. 10.2 Neuropsychological test results

decided to perform a magnetic resonance imaging (MRI), a positron emission tomography (PET), and a liquor examination. Results and pictures are reported in images (Panel a and Panel b, Fig. 10.3).

10.2.3 Conclusions

In conclusion, the patient was diagnosed with "a moderate cognitive deficit of probable primary degenerative nature, such as Alzheimer's disease." Moreover, the neurologist suggested to introduce 5 mg of donepezil daily and to repeat neuropsychological tests after 6 months.

This case describes the situation of a well-known patient with MDD who presents, at some point of her life, different clinical features in her depression. Until 2007 depressive episodes were characterized by mood deflection, apathy, and anhedonia, but she responded to the antidepressant treatment, reaching full recovery. The patient also experienced several years of well-being, without any pharmacological treatment. In 2007, however, she experienced the onset of her memory deficits, which, at the beginning, seemed to be ascribed to memory domain and connected to mood deflection (depressive "pseudodementia"). These deficits, however, did never remit and worsened over time. At this point, the neuropsychologist supposed a cognitive deficit independent from depression (MCI) (Fig. 10.4).

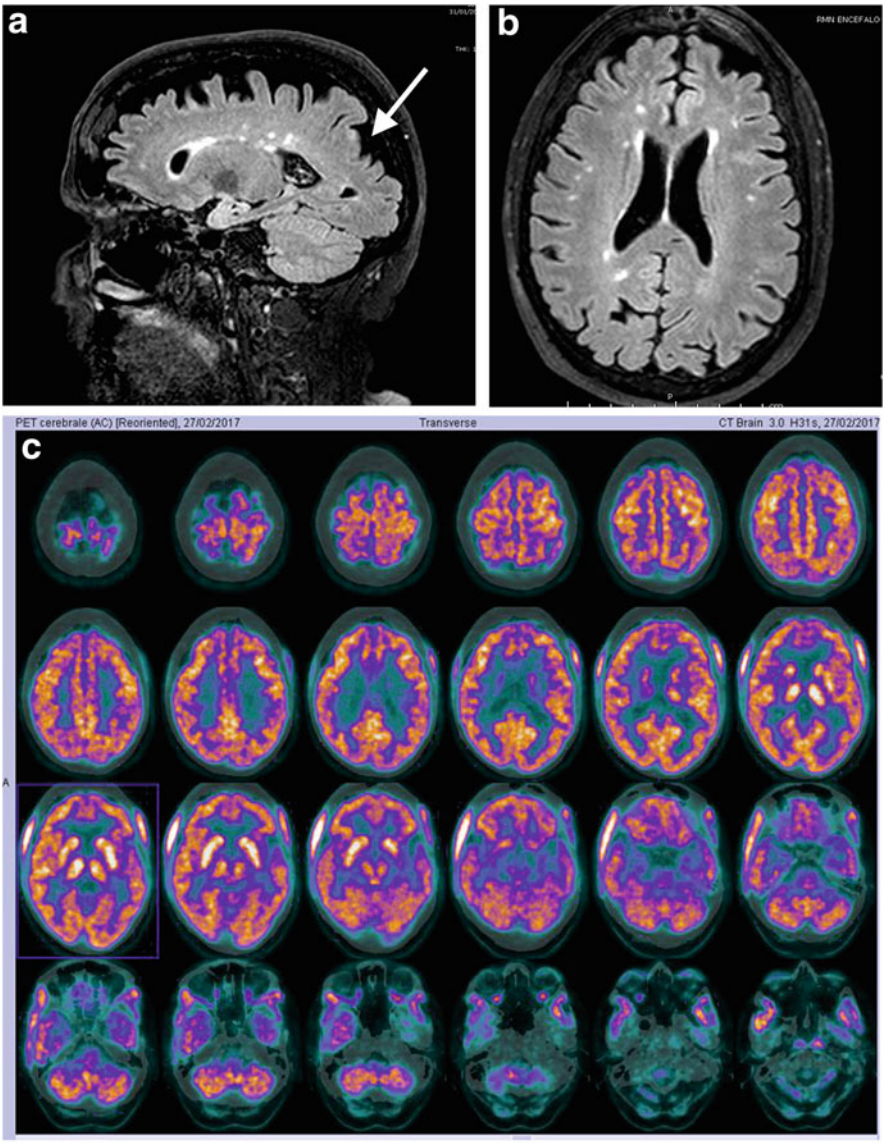
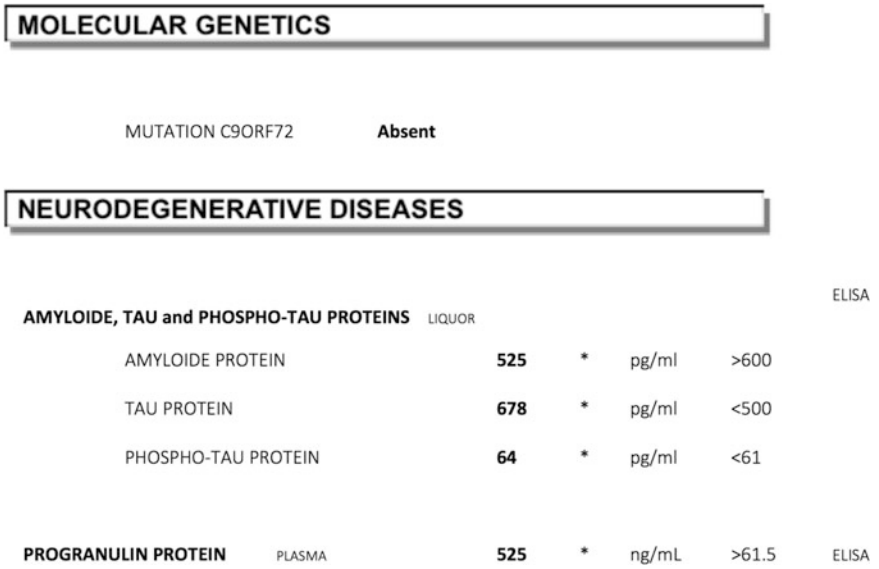


Fig. 10.3 (Panel **a**) T1-weighted sagittal image shows a moderate enlargement of the sovratentorial cortical liquoral spaces. (Panel **b**) T1-weighted sagittal image shows white matter hyperintensities, probably on vascular bases most expressed in the periventricular white matter. (Panel **c**) FDG-PET shows areas of modest reduction of the fixation of the analogue of radiolabeled glucose at the mesial regions of the temporal lobes of both sides, predominantly in the left one



MOLECULAR GENETICS

MUTATION C9ORF72 **Absent**

NEURODEGENERATIVE DISEASES

AMYLOIDE, TAU and PHOSPHO-TAU PROTEINS	LIQUOR					ELISA
AMYLOIDE PROTEIN		**525**	*	pg/ml	>600	
TAU PROTEIN		**678**	*	pg/ml	<500	
PHOSPHO-TAU PROTEIN		**64**	*	pg/ml	<61	
PROGRANULIN PROTEIN	PLASMA	**525**	*	ng/mL	>61.5	ELISA

Fig. 10.4 Liquor examination shows an increase in the abovementioned proteins

In the following years, the patient became amnesic and also unable to cope with her daily activities. She experienced partial disorientation, and she easily lost objects such as keys or forgot to take her medications correctly.

The doubt that the patient showed features of the onset of a degenerative disorder (e.g., Alzheimer's disease) was investigated, and the diagnosis of Alzheimer's dementia was made.

10.3 Literature Review

The described case focuses on the overlap between depression and major neurocognitive disorder in the elderly population. Recent studies tried to determine the relationship between these two diagnoses and comorbidity [31]. Evidence generated different hypotheses. For example, Butters et al. found that depression severity could impact on the threshold of the dementia onset [32], whereas other authors considered dementia/cognitive impairment as features of depression [33] or elderly depression as a prodromal phase of dementia [34]. On the other hand, depression could be a reactive mood disorder due to cognitive decay [35], or the two disorders could share the same risk factors and consequently present common aspects [36–38]. This could justify the increased prevalence of both disorders in the elderly population and their frequent comorbidity. Other potential links between late-onset depression and dementia may be common vascular factors [39–41], because depression has been associated with vascular risk factors and with

cerebrovascular lesions on neuroimaging [1, 42]. Nevertheless, the same vascular lesions are observed in MRI/TC images of patients affected by mild cognitive impairment.

The term "pseudodementia" was coined for the first time by Kiloh in 1961 [43] to describe cases in which depressed patients closely mimed aspects typical of the dementia spectrum. It underlines the overlap between elderly depression and dementia. Dementia and "pseudodementia" share cognitive deficits (e.g., memory, language, speech, executive functions), particularly during the acute phase or after depression, when patients respond to treatment but not fully remit.

Even though performances in neuropsychological tests of depressed patients show some specific characteristics (e.g., long reaction time, deficits spread in different domains with variable severity, time fluctuation of performance), they tend to underestimate their cognitive functioning; it is due to a lack of self-esteem. On the other hand, patients with dementia have no insight of bad performances; they tend to worsen in the same domains, to answer fast and spontaneously; and they overestimate their memory and cognitive functioning. Awareness of memory deficits also seems to be useful to distinguish between depression and mild cognitive impairment (MCI) [44].

However, the main difference is the reversible nature of depressive pseudodementia (the so-called "pseudo" component), whereas the cognitive pattern in dementia tends to become increasingly worse during the following months and years.

In any case, to date, pseudodementia has no diagnostic value and remains a descriptive denomination to describe cognitive deficits observed in psychiatric disorders, in particular in depressive disorders [45].

MCI is characterized by the presence of cognitive concerns, objective evidence of impairment in one or more cognitive domains, preservation of independence in functional abilities, and no dementia [46]. Substantially, the construct of MCI has been considered as a transitional step between normal aging and dementia, for which early preventive interventions may be possible [47]. Over time, this concept has been widely revised; in fact MCI was introduced for the first time in 1988 by Reisberg and colleagues, and it corresponded to stage 3 of the Global Deterioration Scale (GDS), an evaluation scale which rates the dementia state [48]. Then, also the Clinical Dementia Rating (CDR) scale became an instrument to quantify and to describe both mild impairment and very early dementia. However, it has been realized that none of the two rating scales alone could adequately characterize the subtle differences between MCI and the early stage of dementia; indeed, in a study conducted by Brodaty et al. subjects affected by MCI (as currently defined) could be classified as GDS stages 2–3 and as showing a CDR of 0–0.5 [49].

Regarding the diagnostic criteria of MCI, they have been revised in a conference of international experts on MCI [50, 51]. In fact patients with MCI have been observed to be more memory impaired than the cognitively normal subjects, but to present a lower memory impairment than subjects with dementia. However, other (non-memory) cognitive performances only showed minimal alterations in MCI spectrum [52].

In any case, keeping in mind that MCI and dementia are different diagnostic entities, it has been observed that only 16.5% of patients affected by MCI develop dementia in about 12 months [52]. The remaining 83.5% do not progress to a dementia status; so we should consider MCI and dementia as two different diagnoses, in a possible context of continuum, where MCI may imply a further development to dementia or it might imply stability or, unfortunately less commonly, improvement in their clinical symptoms. Consequent relevant clinical implication consists of the possibility of intervention only in the MCI phase in those patients, who are destined to a progressive cognitive decline, with the medical aim of decelerating or arresting further development.

Furthermore, many studies investigated this topic and showed that depression significantly increases the risk for dementia and for prodromal phase of MCI [46, 48, 53]. Consequently, given this correlation, it may be important to understand whether antidepressant treatment alone or combined with other regimens could positively impact on cognition [54]. Finally, a close monitoring of elderly depression may be a possible therapeutic tool for preventing or decelerating the development of dementia.

Regarding the clinical-diagnostic gray area of pseudodementia, many years ago Kaszniak [55] provided an important summary, which clarifies the difficult differentiation between reversible cognitive deficits due to depression and dementia:

- Early signs of a pervasive developmental disorder can easily be confused with cognitive alterations due to old age.
- Cognitive impairment represents a frequent sign of depressive clinical spectrum. It can be severe enough to play a confusing role in the differential diagnosis between dementia and depression.
- Signs of neurologic diseases, associated with progressive decline (i.e., Alzheimer's or Parkinson's disease), show many clinical aspects, which overlap with depression.
- Dementia and depression can be in comorbidity.

Thus, we are not able to exactly address the mechanisms linking depression and dementia, but all previous evidence supports the hypothesis that elderly depression often accompanies cognitive impairment. An interesting study showed how late-life depression quite often co-occurs with cognitive decline, but does not precede it [56].

Regarding the diagnostic pathway, according to recent literature, we underlined the importance of instrumental diagnostic tests, such as CSF laboratory analysis [27], imaging [26], or EEG [29]. In fact, since many clinical aspects could overlap, these second-/third-line procedures could provide objective data, which could help the diagnostic process. Thus imaging, CFS analysis and EEG are useful not only to exclude other pathological presentations but also to recognize the diagnosis of dementia, depression, or both.

Opinions about antidepressant pharmacotherapy in elderly people are not univocal. Antidepressants (ADs) have been found to be protective against dementia [57]. Moreover, AD therapy decreases the risk of developing depressive episodes

associated with cognitive impairment. This pattern was found for both older and last generations' ADs [57]. This concept has been further supported in a study with paroxetine, in which interaction between paroxetine and mitochondrial proteins could play a neuroprotective role [58]. Also fluoxetine has shown to promote both the proliferation and neuronal differentiation of neural stem cells and to have protective effects against various neurodegenerative diseases [59]. Conversely, some authors showed how antidepressant drugs were associated with an increased risk of developing cognitive impairment [60]. Elsewhere, no significant differences between AD treatment and posttrial cognitive functioning suggested cognitive impairment resistance to ADs [61].

New therapeutic strategies for dementia have been widely investigated: they are based on several blood peripheral markers in patients who have cognitive deficits, which could play a causal role. For example, circadian rhythm alterations, immune dysfunction, and/or oxidative stress, which are key pathologic processes involved in depressive cognitive dysfunction and neurodegeneration, could be potential targets for novel treatments [12]. Moreover, interventions on the monoaminergic system (protagonist of the oxidative stress mechanism) could prevent neurodegeneration. Obviously, these are only initial steps for a new treatment, but further research is required to better understand how the cited pathways could impact on the physiopathology of a depressive cognitive impairment/neurodegenerative cognitive decline.

Key Points

- Numerous epidemiological studies demonstrate how, in the next few years, ageing population will reach a higher percentage (approximately 20%). This will result in an increase of incidence and prevalence of progressive cognitive deficits and geriatric depression.
- With the new DSM-5, the term "dementia" was replaced by the concept of "major neurocognitive disorder." The term dementia is still used, especially to classify the various subtypes (i.e., dementia with Lewy bodies).
- Differential diagnosis is crucial with other disorders, which impair mental status (i.e., delirium). Delirium symptoms could mirror those of dementia—often causing misdiagnosis, such as in the case of confusion, loss of orientation, and memory impairment. However, many organic conditions typical of the elderly (hydro-electrolyte alterations, thyroid dysfunction, or any infections) can simulate cognitive degeneration.
- In the differential diagnosis of the geriatric population, it is essential to monitor blood tests and assumption of psychiatric and nonpsychiatric drugs. It is also important to perform a computed tomography or a magnetic resonance imaging, an electroencephalogram, and other second-level tests such as positron emission tomography and cerebrospinal fluid analysis.
- Neurocognitive tests and history of symptoms progression can be useful to make a differential diagnosis between dementia and cognitive deficits secondary to depression.
- Dementia and depression can easily overlap and appear in comorbidity.

- An element that differentiates depression from dementia is the rapid onset of cognitive declines, associated with depressed mood. The depressed subject appears aware of his cognitive symptoms and their severity. On the other side, Alzheimer's dementia progresses slowly, and the patient is unaware of the severity of his deficits.

Self-Assessment Questionnaire

1. What is the most common type of dementia that shows an early onset, compared to the others?
   (A) Alzheimer's disease
   (B) Dementia with Lewy body
   (C) Frontotemporal dementia
   (D) Parkinson's disease
2. Who has been coined for the first ever term "pseudodementia"?
   (A) Kraepelin, 1880
   (B) Kohl, 1961
   (C) Babinski, 1900
   (D) Perusini, 1930
3. What is the main difference between dementia and pseudodementia?
   (A) The reversibility of pseudodementia after treatment.
   (B) The reversibility of memory deficits in dementia patients.
   (C) Mood disorders are more often associated with dementia than pseudodementia.
   (D) Antidepressants don't have any effect in pseudodementia patients, compared to dementia.
4. What, among these, is the cause that most frequently can simulate a delirium in the geriatric population?
   (A) Celiac disease
   (B) Thyroid dysfunction
   (C) Iron deficiency
   (D) Cardiac alterations

References

1. Steffens DC, Otey E, Alexopoulos GS, Butters MA, Cuthbert B, Ganguli M, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. Arch Gen Psychiatry. 2006;63 (2):130. https://doi.org/10.1001/archpsyc.63.2.130.
2. Heser K, Tebarth F, Wiese B, Eisele M, Bickel H, Köhler M, et al. Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). Psychol Med. 2013;43 (8):1597–610. https://doi.org/10.1017/S0033291712002449.

3. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. Arch Gen Psychiatry. 2006;63(5):530–8. https://doi.org/10.1001/archpsyc.63.5.530.
4. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. 2013;202(5):329–35. https://doi.org/10.1192/bjp.bp.112.118307.
5. Mintzer J, Targum SD. Psychosis in elderly patients: classification and pharmacotherapy. J Geriatr Psychiatry Neurol. 2003;16(4):199–206. https://doi.org/10.1177/0891988703258658.
6. WHO-Dementia. World Health Organization endorses global action plan on rising incidence of dementia. Nurs Older People. 2017;29(6):7–7. https://doi.org/10.7748/nop.29.6.7.s6.
7. Espinoza RT. Improving the recognition and management of dementia in long-term care: obstacles and opportunities. J Am Med Dir Assoc. 2006;7(2):128–30. https://doi.org/10.1016/j.jamda.2005.10.002.
8. Fillit HM, Doody RS, Binaso K, Crooks GM, Ferris SH, Farlow MR, et al. Recommendations for best practices in the treatment of Alzheimer's disease in managed care. Am J Geriatr Pharmacother. 2006;4(Suppl A):S9–S28. https://doi.org/10.1016/j.amjopharm.2006.10.001.
9. Pazzaglia P. Clinica Neurologica. 7 edizione. Capitolo "Demenze"; 2012.
10. Roberson ED, Hesse JH, Rose KD, Slama H, Johnson JK, Yaffe K, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology. 2005;65(5):719–25. https://doi.org/10.1212/01.wnl.0000173837.82820.9f.
11. Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain J Neurol. 2003;126(Pt 9):2016–22. https://doi.org/10.1093/brain/awg204.
12. Brown GM, McIntyre RS, Rosenblat J, Hardeland R. Depressive disorders: processes leading to neurogeneration and potential novel treatments. Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;80(Pt C):189–204. https://doi.org/10.1016/j.pnpbp.2017.04.023.
13. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. J Clin Psychiatry. 1999;60(Suppl 20):9–15. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10513852
14. CADTH-Depression. Diagnosing, screening, and monitoring depression in the elderly: a review of guidelines – PubMed – NCBI. Canadian Agency for Drugs and Technologies in Health; 2015. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26468558.
15. Copeland JRM, Beekman ATF, Braam AW, Dewey ME, Delespaul P, Fuhrer R, … Wilson KCM. Depression among older people in Europe: the EURODEP studies. World Psychiatry. 2004;3(1):45–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16633454.
16. Fereshtehnejad S-M, Johannsen P, Waldemar G, Eriksdotter M. Dementia diagnosis, treatment, and care in specialist clinics in two Scandinavian countries: a data comparison between the Swedish Dementia Registry (SveDem) and the Danish Dementia Registry. J Alzheimers Dis. 2015;48(1):229–39. https://doi.org/10.3233/JAD-150144.
17. Miller AM, Begley E, Coen R, Doyle M, Dunne J, Hutchinson S, … Lawlor BA. Clinical consensus guidelines on the application of cerebrospinal fluid biomarkers for Alzheimer's disease diagnosis: recommendations of the Irish network for biomarkers in neurodegeneration. Ir Med J. 2016;109(10):483. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28644588.
18. Hofmann W. Guideline-based diagnosis of dementia etiology. Zeitschrift Fur Gerontologie Und Geriatrie. 2012;45(8):761–71–3. https://doi.org/10.1007/s00391-012-0399-y
19. APA American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-V; 2013.
20. APA American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV; 1994.

21. Gold DA. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. J Clin Exp Neuropsychol. 2012;34(1):11–34. https://doi.org/10.1080/13803395.2011.614598.
22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5349366.
23. Ozer S, Young J, Champ C, Burke M. A systematic review of the diagnostic test accuracy of brief cognitive tests to detect amnestic mild cognitive impairment. Int J Geriatr Psychiatry. 2016;31(11):1139–50. https://doi.org/10.1002/gps.4444.
24. Tsoi KKF, Chan JYC, Hirai HW, Wong SYS, Kwok TCY. Cognitive tests to detect dementia: a systematic review and meta-analysis. JAMA Intern Med. 2015;175(9):1450–8. https://doi.org/10.1001/jamainternmed.2015.2152.
25. Carlesimo GA, Caltagirone C, Gainotti G. The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The group for the standardization of the mental deterioration battery. Eur Neurol. 1996;36(6):378–84. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8954307.
26. Barthel H, Schroeter ML, Hoffmann K-T, Sabri O. PET/MR in dementia and other neurodegenerative diseases. Semin Nucl Med. 2015;45(3):224–33. https://doi.org/10.1053/j.semnuclmed.2014.12.003.
27. Lista S, Toschi N, Baldacci F, Zetterberg H, Blennow K, Kilimann I, et al. Cerebrospinal fluid neurogranin as a biomarker of neurodegenerative diseases: a cross-sectional study. J Alzheimers Dis. 2017;59(4):1327–34. https://doi.org/10.3233/JAD-170368.
28. Società Italiana di Neuroscienze. Expert Panel Alzheimer. Malattia di Alzheimer. Documento di consenso, DSM-V, MMSE, RMN, Liquor, es. ematici per escludere infezioni disdratazione, squilibri elettrolitici, disfunzioni tiroidee; 1999.
29. Neto E, Biessmann F, Aurlien H, Nordby H, Eichele T. Regularized linear discriminant analysis of EEG features in dementia patients. Front Aging Neurosci. 2016;8:273. https://doi.org/10.3389/fnagi.2016.00273.
30. De Carlo V, Calati R, Serretti A (2016). Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. Psychiatry Research. Elsevier Ireland Ltd.
31. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014;79(2):184–90. https://doi.org/10.1016/j.maturitas.2014.05.009.
32. Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, ... Becker JT. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci. 2008;10(3):345–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18979948.
33. Sheline YI, Barch DM, Garcia K, Gersing K, Pieper C, Welsh-Bohmer K, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biol Psychiatry. 2006;60(1):58–65. https://doi.org/10.1016/j.biopsych.2005.09.019.
34. Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry. 2010;18(2):98–116. https://doi.org/10.1097/JGP.0b013e3181b0fa13.
35. Huang C-Q, Wang Z-R, Li Y-H, Xie Y-Z, Liu Q-X. Cognitive function and risk for depression in old age: a meta-analysis of published literature. Int Psychogeriatr. 2011;23(4):516–25. https://doi.org/10.1017/S1041610210000049.
36. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. Acta Psychiatr Scand. 2006;113(5):372–87. https://doi.org/10.1111/j.1600-0447.2006.00770.x.
37. Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. Curr Opin Psychiatry. 2011;24(6):461–72. https://doi.org/10.1097/YCO.0b013e32834bb9d4.

38. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112–7. https://doi.org/10.1016/S0140-6736(05)67889-0.
39. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. Arch Gen Psychiatry. 1997;54(10):915–22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9337771
40. Flicker L. Vascular factors in geriatric psychiatry: time to take a serious look. Curr Opin Psychiatry. 2008;21(6):551–4. https://doi.org/10.1097/YCO.0b013e32830ef736.
41. Teper E, O'Brien JT. Vascular factors and depression. Int J Geriatr Psychiatry. 2008;23(10):993–1000. https://doi.org/10.1002/gps.2020.
42. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and depressive symptoms in elderly adults. Arch Gen Psychiatry. 2000;57(11):1071–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11074873.
43. Kiloh LG. Pseudo-dementia. Acta Psychiatr Scand. 1961;37:336–51.
44. Coutinho G, Drummond C, Teldeschi A, Mattos P. Awareness of memory deficits is useful to distinguish between depression and mild cognitive impairment in the elderly. Rev Bras Psiquiatr. 2016;38(3):231-234. doi: https://doi.org/10.1590/1516-4446-2015-1772. Epub 2016 May 17
45. Kang H, Zhao F, You L, Giorgetta C, Venkatesh D, Sarkhel S, Prakash R. Pseudo-dementia: A neuropsychological review. Ann Indian Acad Neurol. 2014 Apr-Jun; 17(2):147–54. PMID: 25024563.
46. Lara E, Koyanagi A, Domènech-Abella J, Miret M, Ayuso-Mateos JL, Haro JM. The impact of depression on the development of mild cognitive impairment over 3 years of follow-up: a population-based study. Dement Geriatr Cogn Disord. 2017;43(3–4):155–69. https://doi.org/10.1159/000455227.
47. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild Cognitive Impairment. Arch Neurol. 2009;66(12):1447–55. https://doi.org/10.1001/archneurol.2009.266.
48. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. Dement Geriatr Cogn Disord. 2007;25(2):115–26. https://doi.org/10.1159/000112509.
49. Brodaty H, Heffernan M, Kochan NA, Draper B, Trollor JN, Reppermund S, et al. Mild cognitive impairment in a community sample: The Sydney Memory and Ageing Study. Alzheimers Dement. 2013;9(3):310–317.e1. https://doi.org/10.1016/j.jalz.2011.11.010.
50. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183–94. https://doi.org/10.1111/j.1365-2796.2004.01388.x.
51. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256(3):240–6. https://doi.org/10.1111/j.1365-2796.2004.01380.x.
52. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology. 2010;74(3):201–9. https://doi.org/10.1212/WNL.0b013e3181cb3e25.
53. Xu W, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015;86(12):1299–306. https://doi.org/10.1136/jnnp-2015-310548.
54. Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol. 2011;7(6):323–31. https://doi.org/10.1038/nrneurol.2011.60.
55. Kaszniak AW, Fox J, Gandell DL, Garron DC, Huckman MS, Ramsey RG. Predictors of mortality in presenile and senile dementia. Ann Neurol. 1978;3(3):246–52.
56. Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JJ, et al. Late-Life Depression, Mild Cognitive Impairment, and Dementia. JAMA Neurol. 2013;70(3):383. https://doi.org/10.1001/jamaneurol.2013.603.
57. Kessing LV, Søndergård L, Forman JL, Andersen PK. Antidepressants and dementia. J Affect Disord. 2009;117(1–2):24–9. https://doi.org/10.1016/j.jad.2008.11.020.

58. Steiner JP, Bachani M, Wolfson-Stofko B, Lee M-H, Wang T, Wang T, et al. Interaction of paroxetine with mitochondrial proteins mediates neuroprotection. Neurotherapeutics. 2015;12 (1):200–16. https://doi.org/10.1007/s13311-014-0315-9.
59. Chang K-A, Kim JA, Kim S, Joo Y, Shin KY, Kim S, et al. Therapeutic potentials of neural stem cells treated with fluoxetine in Alzheimer's disease. Neurochem Int. 2012;61(6):885–91. https://doi.org/10.1016/j.neuint.2012.03.017.
60. Tifratene K, Robert P, Metelkina A, Pradier C, Dartigues JF. Progression of mild cognitive impairment to dementia due to AD in clinical settings. Neurology. 2015;85(4):331–8. https://doi.org/10.1212/WNL.0000000000001788.
61. Halahakoon DC, Roiser JP. Cognitive impairment in depression and its (non-)response to antidepressant treatment. Evid Based Ment Health. 2016;19(4):e23–e23. https://doi.org/10.1136/eb-2016-102438.