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Updated Information on Some Cognitive Disorders

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Additional information is available at the end of the chapter

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Abstract

Dementia is a neurodegenerative disorder characterized by a progressive decline in cognitive and daily living activities. The present review aimed to highlight the most relevant and updated information available in the medical literature on mild cognitive impairment, Parkinson's dementia, Alzheimer's disease, vascular dementia, normal pressure hydrocephalus, and Wernicke-Korsakoff and to deliver some personal observations about cognitive disorders and dementia.

Keywords: dementia syndrome, Alzheimer's disease, frontotemporal dementia, vascular dementia, normal pressure hydrocephalus, Wernicke-Korsakoff, alcohol-related dementia, Parkinson's dementia, mild cognitive disorder

1. Introduction

Disorders of cognition have been identified since the beginning of the humankind, and since then, different types of clinical presentation have been reported. The same happened with the clinical manifestations of dementia.

Dementia is a neurodegenerative disorder characterized by a progressive decline in cognitive and functional abilities. This neurodegenerative process has multiple causes, clinical manifestations, and heterogeneity with respect to the impact of sex or gender on prevalence, risk factors, and outcomes [1–3].

In 2015, it was estimated that there were 46.8 million people with dementia worldwide, of whom 58.0% were living in low- and middle-income countries, and that there were annually 9 million new global cases of dementia.

The estimated prevalence of dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, and 6.4% at North America. Currently, the number of patients with dementia is projected to increase to 131.5 million by 2050 [4].

Apart from some neuropsychological test that we will describe at the end of this chapter, there are some radiological investigations that can help in increasing the certainty of dementia diagnosis. A positron emission tomography (PET) scan and a special form of MRI can more

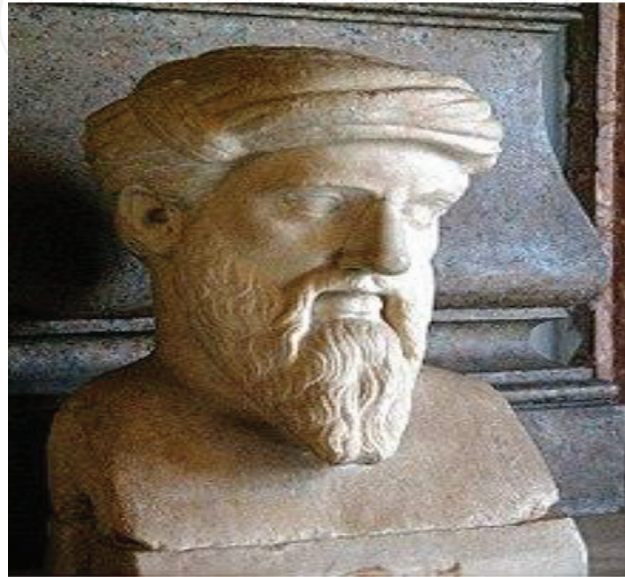


Figure 1. Pythagoras of Samos (c 570 BC–c 495 BC).

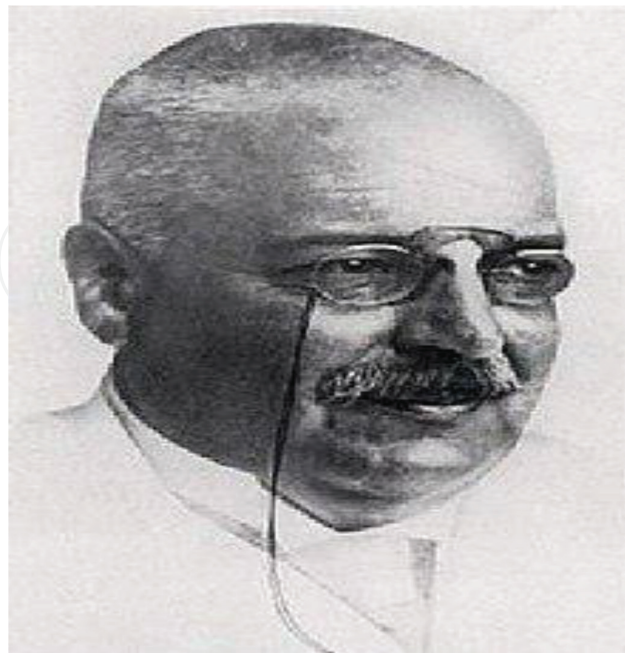


Figure 2. Alois Alzheimer 1864–1915 from Bavaria.

definitively confirm the diagnosis of various types of dementia and raise the accuracy of the diagnosis to 90%. A PET scan administered and reviewed by an expert delivers the most accurate and suggestive results while diagnosing dementia. The most accurate form of PET scanning for types of dementia is called stereotactic surface projection, which involves an advanced statistical analysis of the data.

We did a bibliographic investigation, and then the PubMed, Embase, and Web of Science were searched. In this chapter, we comment about some types of dementia and cognitive impairment according to the available publications in the medical literature, and we also delivered some comments based on our clinical observation from working with affected patients in Mthatha (one of the rural areas of South Africa) over the past 21 years.

The first man who made allusions to dementia at the seventh-century BC was the Greek philosopher Pythagoras (**Figure 1**) followed by Solon, Aristotle, Plato, Cicero, Galen, Celsus, Roger Bacon, and others. That related cognitive dysfunction with the aging on the brain is not well described until 1906, when Alois Alzheimer (**Figure 2**) found at postmortem brains of affected younger people, with dementia symptoms the microscopic plaques and tangles now known as hallmarks of the disease.

2. Novel information on mild cognitive impairment

The concept of MCI is described in the nineteenth century when loss of recent memories was documented as the first sign of dementia [5]. Some degree of cognitive disturbance was thought to be part of normal aging, and then various names were used to define it such as (1) age-associated memory impairment, (2) age-associated cognitive decline, and (3) benign senescent forgetfulness [6, 7].

In 1980, with the arrival of new neuropsychological test to measure subjective and objective cognition, an intermediate phase between normal aging and dementia became more widely accepted [8]. At that time, it was defined as the presence of subtle deficits in cognition with some impairment in executive function. Following an expert international conference, all previous definitions and the way of diagnosis and management of MCI were better performed [9, 10].

Historically, the term MCI has been in the literature for almost four decades, with the initial use coming from investigators at the New York University who referred to stage 3 on the Global Deterioration Scale as being MCI [11].

In 1999, some authors at the Mayo Clinic reported subjects in their community aging study presenting a memory problem beyond what was expected for age and who demonstrated a MCI (by neuropsychological test) yet did not meet criteria for dementia [12].

The prevalence of MCI is estimated around 3–19% in the elderly people. However, in a community setting, 44% of people with MCI returned to normal after 1 year [13].

Conversion rates to dementia vary according to the setting, with 11–33% conversion over 2 years [14].

In 2015, other authors demonstrate that females with MCI have greater longitudinal rates of cognitive and functional progression than males [15].

Gauthier et al. [9] also defined MCI as a syndrome of cognitive decline, which is greater than would be expected for an individual's age and level of education but does not impede the individual's ability to perform daily activities of normal life.

Most of our patients presenting MCI had behavioral changes, depression, anxiety, and apathy, and most of them were full aware on their condition and personal frustrations, and their daily skills and activities necessary for independent daily living within the home and their communities such as dressing, grooming, ambulating, feeding, bathing, continence, transferring, and toileting were not affected. However, some authors have report that MCI patients may have difficulties in performing instrumental activities such as cooking, shopping, cleaning, laundry, driving, self-medication, and making call telephonically, among others, comparing to age-matched normal cognitively people [16, 17].

The Mayo Clinic criteria previously cited have been focused on a memory disorder and were delivered to clarify the earliest symptomatic stages of AD. However, soon later, it was well established that not all intermittent cognitive states were due to incipient AD and not all patients have just a memory impairment. To solve this dilemma, the Key Symposium was held in Stockholm, Sweden, in 2003, and in 2004, broad scope and other goal were delivered [18, 19].

Including a broad classification scheme beyond memory, the recognition of MCI could result from multiple causes and not just AD.

The Key Symposium characterization has been very useful in our practice and allowed us to distinguish the amnestic form of MCI from the nonamnestic ones, among other benefits.

Recently, Su et al. demonstrated that CA1 atrophy and subiculum thinning is significantly greater in AD and MCI patients than their control group, but similar between MCI and AD, as have been reported in previous investigations. It is proved that CA1 and subiculum changes at the hippocampus occur early on these pathologies [20].

Numerous international studies have been completed involving several thousand subjects, and these studies tend to estimate the overall prevalence of MCI in the range of 12–18% in persons above the age of 60 years. Lifestyle modifications and other nonpharmacologic therapies have been investigated by Petersen who found that aerobic exercise may be effective at reducing the rate of progression from MCI to dementia. Criticism has been raised regarding the boundaries of the condition of MCI with respect to differentiating it from changes of cognitive aging and also differentiating it from dementia [21].

Biomarkers provide a path toward the early detection of people at high risk for cognitive disorder and thereby its early prevention and/or management. *Nevertheless, these advances, whether for PD or AD, came with some risks and limitations that should to reconcile the potentially negative aspects of early diagnosis, the risk-benefit ratios of various treatments, and accessibility of biomarker testing and clinical resources, counseling, and ways of therapies once available* [22].

MCI is well represented in our series PD, and in our opinion, Parkinson's disease-cognitive rating scale seems to be more selective in detecting MCI and PDD than Montreal Cognitive Assessment.

Plasma α -synuclein level was not associated with the presence or type of cognitive impairment, but the *ApoEe4* allele carrier status was significantly associated with executive dysfunction in PD, and both depression and diabetes mellitus are well known as risk factors for cognitive impairment [5].

The biomarkers of cognitive disorder in patients with diabetes can be grouped according to the following three aspects:

1. Functional or metabolic changes by neuroimaging tools
2. Serum molecules or relevant complications
3. Genetic types

In diabetic patients with cognitive disorder such as specific factors related to associated depression, inflammation, poor glucose metabolism, insulin resistance, micro/macrovascular complications, neurotrophic molecules, adipokines, and Tau protein presented remarkable changes. In diabetic patients, some neuroimaging studies provide more information on functional, structural, and metabolic changes during the cognitive decline progression [23].

Publications from several authors suggest that greater degrees of atherosclerosis of the carotid artery are associated with the progression from MCI to dementia [24, 25].

In another study, the authors demonstrated that alterations in the intima media thickness (IMT) of the common carotid artery and the number of plaque (confirmed by ultrasound) are associated with an increased risk of MCI and dementia. In MCI, the IMT was more frequently observed, whereas in patients with dementia, the most common finding was increased numbers of carotid plaques. These researchers suggest that their findings may aid in identifying elderly people at higher risk for the progression of MCI when morphological impairment of cerebrovascular structures has been identified. In other words, the presence of atherosclerotic changes and modifications in blood factors such as p-selectin glycoprotein ligand, platelet-leukocyte aggregates, and platelet-monocyte aggregation can be used to predict MCI and dementia [26].

Some authors introduced a novel methodology to get an accurate classification of patients with AD or MCI from cognitively unimpaired (CU) people for clinical diagnosis and adequate intervention, respectively. These researchers focused on differentiating AD or MCI from CU based on the multifeature kernel supervised within-class-similar discriminative dictionary learning algorithm confirmed that methodology had superior performance in face recognition. They also included structural MRI, fluorodeoxyglucose PET, and florbetapir-PET data from the Alzheimer's Disease Neuroimaging Initiative database for classification of AD versus CU, MCI versus CU, as well as AD versus MCI, successfully [27].

Tai Chi is a type of mind-body exercise that combines physical and cognitive-stimulating activity that provides good benefits on general cognition and instrumental activities of daily living in patients with MCI [28].

Mueller et al. [29] have documented spoken language as a noninvasive, multidimensional, and informative biological sample for the early diagnosis of AD, primary progressive aphasia, and other cognitive disorders. They also confirmed that connected language analysis is one of

the most promising state-of-the-art diagnostic tools for MCI. Their results provide evidence that features of connected language are associated with very early, subclinical memory loss in late-middle age. This study helped toward a better comprehension of early language dysfunction associated with a cognitive decline.

Recently, Shang et al. [30] investigated differences in plasma fatty acids, adiponectin, leptin, plasma markers of inflammation, serum amyloid A, plasma lipids, and low-density lipoprotein in patients with AD, MCI, vascular dementia, and ischemic stroke in comparison to normal controls. They found different levels in almost all patients, indicating that these diseases have diverse pathological mechanisms.

The evaluation of inner retinal layers as a biomarker of MCI has brought more novel information about the possibility to predict cognitive decline, which can be used as prognostic information for patients who need to take financial and family decisions, advanced directives, afford care/residence decisions, etc. This reliable prognostic information and planification of the future will serve as significant societal benefit, taking into account the high societal cost of cognitive disorder care all over the world [31].

The level of relationship between cognition and functional outcomes in the MCI population is affected mainly by cognitive domains and a little bit by age and educational level. Early identification of subtle functional disturbance in MCI and comprehension of its cognitive and noncognitive correlates are determinant in the diagnostic process because of its prediction for dementia progression [32].

A recent meta-analysis investigation showed that hearing impairment is associated with a higher risk of MCI and dementia in elderly people [33].

Recently, a group of Korean researches have confirmed that a dietary pattern based on seafood and vegetables in older Korean adults can reduce MCI remarkably [34].

Recent study made by Correa-Jaraba and colleagues confirmed that the event-related potential technique is useful for evaluating changes in brain electrical activity and increased amplitude of the P3a component is a novel neurocognitive marker for differentiating amnesic MCI [35].

On the other hand, it seems to be that telerehabilitation by videoconference can improve cognitive function in patients with MCI, but this procedure needs more investigation to confirm its feasibility [36].

Three months ago, some investigators documented the association between the presence of hallucinations, delusions, anxiety, depression, and abnormal motor behavior, with the risk of developing incident dementia, *independent of other known risk factors, including MCI in the future, a simple, low-cost strategy for screening population groups at dementia risk, particularly in environments with limited access to specialized services and very sophisticated resources* [37–40].

3. Some comments about Alzheimer's disease

Alzheimer's disease is a progressive nonreversible neurodegenerative disorder, characterized by cognitive decline including learning capacity, emotional and behavioral alterations, motor

skills impairment, including dysfunction of the autonomic nervous system and desynchronization of circadian rhythms. According to Picard et al. [41], early-onset Alzheimer's disease (EOAD) and behavioral variant frontotemporal dementia (bvFTD) are the most common types of presenile neurodegenerative dementia (i.e., age at onset around 65 years old). Compared to the typical episodic memory dysfunction of late-onset AD, EOAD patients show a constellation of multidomain deficits at presentation, which can include not only memory, but also language, executive, visuospatial abnormalities, and behavioral disturbances like bvFTD cases [42].

Volumetric and cortical thickness studies have shown a prevalent involvement of posterior parietal regions in EOAD and of anterior fronto-insular-striatal areas in bvFTD [43, 44]. Some studies reported a greater white matter (WM) involvement in bvFTD compared to EOAD [45–50]. Filippi et al. and Zhou et al. [51, 52] found a divergent pattern of altered functional connectivity in the default mode network (DMN) and salience network comparing EOAD and bvFTD patients.

Some specialists from Alzheimer's Association consider that AD is the underlying cause of all types of dementia, and it is characterized by β -amyloid plaques, neurofibrillary tangles, and neurodegeneration in areas of the brain associated with cognition, such as the cortex and hippocampus. AD is also characterized by disturbances of the daily activities involving memory, speech and language, reasoning, planning, and other cognitive abilities [53].

The Framingham Study, which followed up 2611 cognitively intact participants (1550 women and 1061 men) on many for 20 years, indicated that risk factor for AD in 65-year-old woman was almost twice that of men [1] because it seems to be that life expectancy is longer in ladies. Other epidemiologic investigations also confirmed that neurodegeneration develops more rapidly in females who are often diagnosed earlier than males [54, 55]. And they are often diagnosed earlier in the course of illness than men. In many cases, inflammation is another risk factor for AD that dysregulated neuroinflammatory reaction is another possible AD etiology, which is more pronounced in females [56, 57].

Some research suggests the important of sex differences in microglia development and in response to fluctuating gonadal steroids during the life and there are more microglia in female than males [58]. Females have been shown to have more microglia than males [1].

Apart from the previous statements, some authors suggest that particular aspects of music perception such as pitch pattern analysis may open a channel on the processing of information streams in major dementia syndromes. Therefore, the potential selectivity of musical deficits for particular dementia syndromes and particular dimensions of processing warrants further systematic investigation [59].

Between classical thiamine deficiency and Alzheimer's disease (AD), many similarities exist and in both are associated reductions in brain glucose metabolism with cognitive deficits. Vitamin B1-dependent enzymes are critical components of glucose metabolism that are reduced in the brains of AD patients and by thiamine deficiency, and their decline could account for the reduction in glucose metabolism [59]. Nevertheless, many other conditions not related with AD can cause dementia as well, and it should be taken into account in the process of diagnosis and management. As the reader can see below, apart from AD, other types of dementia and their etiology are also listed.

In the past decade, we applied the term “mild cognitive impairment (MCI) due to AD” to refer to the symptomatic prodementia phase of AD; in other words, patients with cognitive decline whose primary underlying pathophysiologic was AD but no evidence of a remarkable impairment in social or occupational activities; currently, we separate those patients in two groups.

Typically, amnesic MCI is the type of prodromal stage of dementia due to AD, but other phenotypes can also mimic to this kind of dementia, such as posterior cortical atrophy (also known as the visual variant), logopenic aphasia, or a frontal lobe-dysexecutive presentation of AD. Therefore, as a general agreement, not all MCI is early AD. The Key Symposium characterization of MCI helps to differentiate between the amnesic form of MCI and the nonamnesic one. These clinical syndromes appeared to be aligned with causes in a differential fashion and may have variable outcomes [60]. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) criteria are useful in prediction of amnesic MCI progression to AD, including medial temporal lobe atrophy and hypometabolism in MRI and FDG-PET, respectively [10, 61, 62].

Recently, some researchers reported that plasma total tau and pTau181 levels were higher in AD dementia patients than those in cognitively unimpaired. Plasma pTau181 was more strongly associated with both A β and tau PET. Plasma pTau181 was a more sensitive and specific predictor of elevated brain A β than total tau and better than the combination of age and apolipoprotein E, and they concluded that plasma pTau181 may have utility as a biomarker of AD pathophysiology and as a noninvasive screener for elevated brain A β [63].

Few weeks ago, some authors have found that [^{18}F]AV-1451 uptake showed the strongest regional correlation with hypometabolism. Correlations between [^{18}F]AV-1451 uptake and both hypometabolism and cortical thickness were stronger in participants with greater cortical tau severity. In addition, age, tau asymmetry, and clinical diagnosis influenced the strength of the correlation between [^{18}F]AV-1451 uptake and cortical thickness. Therefore, all these findings support a close relationship between tau and hypometabolism in Alzheimer’s disease but show that correlations between neuroimaging modalities vary across participants [64].

Some investigations have confirmed that people with MCI and a positive amyloid PET scan are more liable to progress rapidly and, again, ADNI data confirmed this. Nevertheless, it is well known that carriers of the apolipoprotein E4 (*APOE4*) genotype are more susceptible to progress rapidly; however, in clinical practice, *APOE* testing did not contribute remarkable to the diagnostic assessment [65].

The study done by Hansson and colleagues relieved more information with regard to these data and corroborates the suspicion that those individuals, particularly with amnesic MCI presenting low CSF levels of A β_{42} and elevated total tau and phosphorylated tau, are at the higher risk for progressing faster than those patients with the same clinical phenotype but normal biomarkers on the CSF [66, 67].

All people presenting a mild cognitive impairment in our series did not present an early Alzheimer’s disease later.

The criteria for MCI due to AD developed by the National Institute on Aging and the Alzheimer’s Association essentially adopted the Key Symposium criteria and explained more explicit some of the diagnostic features. These criteria also considered biomarkers for underlying AD’s pathophysiology trying to define the underlying cause and, hence, predict outcome.

Now, the pathological criteria for AD require the presence of A β deposition in plaques and tau deposition in neurofibrillary tangles. The absence of biomarkers of A β deposition strongly suggests that AD is not the cause of MCI.

The definitive absence of evidence of either A β deposition strongly suggests that the MCI syndrome is not due to AD. This marker analyses the lower A β_{42} levels on CSF [68] and the evidence of A β deposition, using a variety of specific ligands in PET scan [69] and the increased accumulation of tau or phosphorylated tau in the CSF is another biomarker [68].

AD and atrophy in entorhinal cortex (ERC), the hippocampus, and its subfields Cornu Ammonis 1(CA1) and subiculum are simultaneous, and these abnormalities can predict conversion from MCI to clinical AD. It has been documented that in the early stages of AD, some changes at the stratum radiatum, lacunosum, and molecular involving ERC and CA1 can be observed [70].

Lewy body dementia and other types of cognitive disorder are not included in this revision due to limitation of space.

4. Some information about Parkinson's disease

Parkinson's disease (PD) is an idiopathic type of parkinsonism, which progresses gradually in spite of the medical or surgical treatment implemented and it is characterized by bradykinesia, tremor at rest, gait disturbance, postural problems, rigidity, dysarthria, dysfunction of the judgment, reasoning, memory, depression, anxiety, insomnia, and cognitive decline due to loss of midbrain dopaminergic neurons in the pars compacta of the substantia nigra and consequent loss of dopamine input to the caudate nucleus and putamen (striatum), and it is more prevalent in men, whereas rigidity, difficulties pertaining to daytime sleepiness, dribbling saliva, interest in sex, and problems having sex are more common among men with PD [71].

Dementia affected almost 50% of our patients with PD within the first decade after diagnosis is made, but the intensity of their manifestations varied considerably among them. Prospective investigations reveal patient differences in the progression of cognitive deficits and in risk factors for developing PD dementia (PDD) [72].

Identifying patients at risk of dementia and those at the earliest stages of cognitive involvement is important for three important reasons:

1. As new disease-modifying treatments in Parkinson's are emerging, early intervention to slow or prevent Parkinson's dementia is becoming a realistic prospect.
2. Earlier detection of cognitive involvement offers the hope of prognostic information.
3. Finding the earliest features of cognitive involvement may provide insights into underlying mechanisms of disease progression, ultimately leading to identification of novel therapeutic targets [73].

The concept of MCI is introduced in the 1980s, and it is characterized mild cognitive deficits that did not qualify to a diagnosis of dementia in patients with AD, and more recently, it was also introduced for patients with PD [5].

As far as we remember, the concept of “mild cognitive impairment” as a transitional or pre-dementia state in Parkinson’s disease was delivered before 2014, and we also believe that PD-MCI is a transitory stage between normal cognition and dementia.

A recent study showed a strong correlation between the extent of neurofibrillary tangles and alpha synuclein [74]. It seems to be that the insula lobe is one of the vulnerable regions by alpha-synuclein deposition.

The treatment of cognitive symptoms has shown some good results with the introduction of cholinesterase inhibitors (ChEIs) that is more effective in PDD, compared to AD, because of their early, prominent CNS cholinergic disturbance [75].

Rivastigmine has been approved by the United States and European Union for the treatment of PDD with promissory results, while levodopa and other dopaminergic medications are still effective for tremor and parkinsonian motor symptoms of PDD. For the treatment of psychotic manifestations, atypical antipsychotics (e.g., quetiapine, clozapine) have been used in PDD. There is current evidence-based medicine favoring clozapine in PDD [76].

Novel information about imagenological assessment of PDD is positron emission tomography (PET) scan using C-labeled radiotracer Pittsburgh compound B that has been widely applied for the in vivo assessment of amyloid- β (A β) deposition in patients with AD, with successful results [77, 78].

Progressive supranuclear palsy is included in the classification of Parkinsonism and is also a form of dementia that is characterized by vertical gaze palsy, falling backward, hypokinesia, rigidity, irritability, dysphagia, dysarthria, apathy, depression, and cognitive decline, which is sometimes misdiagnosed as PD. Based on clinical observations from our series of patients with Parkinsonism, neuropsychologically assessed at the early to moderate stages, cognitive decline was a common problem found and some of those patients developed dementia with reduction of quality of life and functional disability. However, an important number of patients presenting mild cognitive impairment (MCI) did not develop dementia up to date. Because we have not resting-state functional MRI (rs-fMRI) facilities in our setting, we could not document the expected structural and functional connectivity alterations of the brain. Recently, some author confirmed that the temporal connectivity alterations found in patients with PD and PD-MCI could be related to the presence of cognitive impairment in PD [79].

5. Updated information on idiopathic normal pressure hydrocephalus

Idiopathic normal pressure hydrocephalus (iNPH) is an important geriatric disease, a treatable cognitive disorder, which can be reliably diagnosed with an organized approach, and its prevalence is expected to increase gradually. This type of hydrocephalus is characterized by late-onset, surgically treated progressive neurodegenerative disease caused by inadequate cerebrospinal fluid (CSF) dynamics and ventriculomegaly, while other types (including low-pressure hydrocephalus) are usually secondary to head injury, subarachnoid hemorrhage,

infections, and other disorders that cause an accumulation of the cerebrospinal fluids (CSF) in the ventricular system of the brain mainly associated to its impaired drainage [80]. Approximately 700,000 persons may have iNPH in the United States. Neuroimaging with either CT or MRI is required for the diagnosis of iNPH [81].

The iNPH, the most common form of hydrocephalus in adult's population, affects the brain parenchymal on the cerebral hemisphere causing cognitive dysfunction, lack of balance, urinary urgency with or without incontinence, problem-solving disabilities, dysarthria, and apraxia of gait apart from spasticity, hyperreflexia, and other upper motor neuron signs.

Gait apraxia is typically the first and worst disturbance in patients with iNPH. The overall prevalence of iNPH ranges from 0.02% to up to 5.9%, depending upon age and specific population studied [82, 83]. Another author reported a prevalence about 0.51–2.9% in the elderly population [84]. Some authors found that the male-to-female ratio for those with idiopathic NPH (iNPH) is 1.39:1 ($P < 0.0001$), and the corresponding incidence rate ratio between males and females with iNPH is 1.838 ($P < 0.0001$), indicating that iNPH is almost twice as likely to occur in older males than older females [85].

In patients presenting Huntington disease with an associated inability to walk or rapid progression of their symptoms, a diagnosis of iNPH should be considered, and they are going to improve the cognitive disorder, gait, and chorea after the lumbar puncture and surgical treatment [86].

Mild apathy is the more common neuropsychiatric symptom in patients with iNPH, and the frontal lobe pathology is the main cause of increased correlation between neuropsychiatric symptoms and cognitive impairment [87].

MCI is quite common presentation in patients with iNPH, and their neuropathological findings are generally consistent with white matter damage, regardless of the underlying, yet unknown, pathophysiological mechanisms [88–92].

Diffusion tensor imaging (DTI) is a useful MRI technique that can reflect the structural integrity and interstitial space of the white matter by detecting the directionality of extracellular water diffusion [fractional anisotropy (FA)] and of free water diffusion [mean diffusivity (MD)] and has been applied to evaluate white matter damage in iNPH [93–96]. Some authors have confirmed that after shunt surgery in patients presenting iNPH, the fractional anisotropy (FA) in the corona radiata decreases, and the regions involved were located between the enlarged lateral ventricles and Sylvian fissures. The plasticity of the brain for mechanical pressure from the CSF system is also confirmed by their findings [97]. An interesting exception found in iNPH is the increased FA within the corticospinal tract [98–102].

Treatment outcome can be predicted by quantitative image biomarker from diffusion MRI, which also serves to distinguish between reversible and irreversible changes in iNPH [103].

Alzheimer's disease can be differentiated from iNPH by cerebral retention of Pittsburgh compound B (PIB: *N*-methyl-[^{11}C]-2-(4-methylaminophenyl)-6-hydroxybenzothiazole) in positron emission tomography (PET) because in iNPH it was limited to the high-convexity parasagittal regions, whereas in AD it spreads over the frontal and temporoparietal lobes. Therefore, the

PIB-PET is very useful in the differential diagnosis between iNPH and AD. Kondo et al. have demonstrated that 3 of 10 (30%) patients with iNPH without any clinical signs of AD had obvious cortical retention in PIB-PET, indicating that iNPH is one of the PIB-positive diseases [104].

In 2016, several studies on iNPH were published in the medical literature [105]. Below, interested readers can find a summary from the most relevant conclusions.

There is no standardization of care or differentiation between various types of hydrocephalus among the confirmed cases of hydrocephalus in the Middle East.

The most common complication seen in postshunting surgery is subdural hematoma, and it shows reduced and even worsening of gait in iNPH.

Remarkable improvements in gait and clinical outcome are seen in patients presenting iNPH after shunting surgical procedures.

After 6 months of shunt surgery in patients presenting iNPH, the best test for identifying clinical improvements is the European-iNPH scale.

Some authors have demonstrated that the vascular brain expansion (during cardiac cycle) is quickly compensated by CSF volume flush, toward the spinal compartment due to a decreased spinal canal compliance, a decreased vascular brain expansion, or an increase of subarachnoid space resistance to CSF flow.

Based on the knowledge that venous drainage helps to control intracranial pressure, some authors have highlighted the potential role of the right side of the heart and the jugular vein valves in the physiopathology of the intracranial pressure.

In iNPH, the main goal of shunt therapy is to improve the patient's mobility and a mean improvement of 0.4 mph has been confirmed.

Dr. Hakim described the iNPH for the first time in 1964, but its physiopathology was not satisfactorily elucidated as yet. Although changes seen on the brain parenchymal after shunt surgery have not been documented, it seems to be that a number of patients with cerebral atrophy could be presenting a reversible subarachnoid augmentation.

At the present moment, reliable biomarkers for selection of iNPH patients for shunt therapy and T-tau or A β -42 for predicting shunt responsiveness are not available and need to be identified. Nevertheless, some potential microRNA biomarkers in the CSF are useful to differentiate iNPH patients from other presenting overlapping symptoms of other disorders such as AD, PD, and progressive supranuclear palsy.

A possible genetic component involved in the pathogenesis of iNPH may be present.

In iNPH patients, the endoscopy third ventriculostomy is also a choice of treatment although some authors have found that it is not effective in treatment of iNPH [106, 107].

Ventriculoatrial shunt (VAS) is another choice of treatment of iNPH, and some authors recommend it as a first choice because it is more physiological, no cardiopulmonary complications have been reported, and less shunt malfunction in the follow-up is found.

The CSF tap test shows good results for diagnosis of iNPH, but its accuracy is not certain, even for bedridden patients, indicated.

The relationship between radiological markers and mortality rate in iNPH is unknown. However, in AD and VaD, the radiological findings are related with high mortality.

A possible comorbidity between FTD and iNPH is suspected because the prevalence of the C9ORF72 is greater than expected.

The genetic and pathophysiological mechanism in AD and iNPH are completely independent.

Sometimes, the best selection of iNPH patients for VPS can be very difficult, but the CSF tap test by removing 30–50 ml of CSF can be used as prognostic test for shunt surgery outcome, but its negative predictive value is not certain. The most common interval between the LP and the formal follow-up examination is between 2 and 4 hours, and nauseous vomiting and headache are less frequent in iNPH patients than the other ones. Shunt surgery is not contraindicated in patients under antithrombotic therapy, and neurotoxic proteins in CSF can be removed from the brain and also improve learning, retention, and delayed recall of verbal memory. The vast majority of patients improve some memory functions [108].

After shunt surgery, some patients do not get the proper regular follow-up by their attending neurosurgeons apart from the first checkout surgical wound and are seen again when the shunt mechanism has failure (i.e., overdrainage due to shunt setting that is too low); patients develop some complication or neurological manifestations (headache that worsens with sitting and standing and improves when lying down) and pain or discomfort from the shunt components, including abdominal pain that requires surgical approach or risk of shunt infection. Longitudinal care can be provided by neurologists if they are well trained. Some adjustable shunts can be affected by strong external magnetic fields [81].

Apart from iNPH patients with depression, the associated presence of delirium, hallucinations, visual or auditory agnosia, impaired naming, anosognosia, failure to recognize close relatives, families, and friends suggest a comorbidity with other types of dementia or neurological disorder [109].

Obviously, in patients presenting dilatation of the ventricular system with an associated cognitive decline only or even only urinary incontinence, the attending doctor should search for another neurological disorder before considering iNPH mainly in those patients without gait disturbances. In cases presenting delirium and ventriculomegaly, the underlying cause of the delirium should be found, treatment initiated, and the patient must recover and return to a stable baseline before looking for iNPH [81]. Currently, the iNPH is the only type of dementia that has an effective treatment for slowing its progression or for curative purposes.

6. Frontotemporal dementia

Frontotemporal dementia (FTD) is a common neurodegenerative disease associated with progressive atrophy of the frontal and temporal lobes, leading to changes in personality,

behavior, and/or speech and language disorder. FTD is less common than the before-mentioned dementias. Among these clinical presentations, Pick's disease is the most common type of presentation due to damage on the frontal and temporal lobes characterized by behavior and personality (apathy) disorders, which usually precede memory loss and dysarthria.

Sometimes, clinical manifestations such as behavioral and personality changes, psychomotor slowness, and decline in executive functions can be seen in both iNPH and behavioral FTD (BvFTD) at the same time and indistinctly [110], and other neuropsychiatric symptoms are frequently detected in both diseases [111, 112] including mania, aggression, disturbances of impulse control, obsessive-compulsive disorder, and psychosis, including paranoia and hallucinations [113–115]. It is well known that personality changes, impulsive behavior, apathy, decreased social interest, and executive dysfunctions, including impairment in solving problems and inhibitory control, are typical manifestations of BvFTD [116]. Almost one-half of patients with frontotemporal lobe degeneration (FTLD) have a familial component, and some authors have found mutations in microtubule-associated protein tau, progranulin, and expanded hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 (C9ORF72) as a common cause of the problem [117]. The expansion of C9ORF72 as a major genetic cause of FTLD has been confirmed by others [118]. On the other hand, Majounie et al. [119] reported that the C9ORF72 repeat expansion is the highest in Finland and is present in about 48% of familial FTLD.

Amyotrophic lateral sclerosis (ALS) is the most common motor presentation associated with the C9ORF72 expansion, but extrapyramidal symptoms have also been documented [120–122]. Fifty percent of patients with ALS exhibit frontal executive deficits during the course of their disease representing the comorbidity of FTD-ALS and associated delusional disorder.

To distinguish BvFTD from iNPH can be a very difficult task considering that both have similar clinical manifestations. Extrapyramidal clinical manifestations of parkinsonism are predominant in patients with BvFTD [117]. Apart from disorder of gait, other remarkable symptoms of iNPH are balance disturbances and psychomotor slowing [123]. Deficits in executive functions are core cognitive changes in both iNPH and BvFTD [116, 123].

Some authors have confirmed in large studies that the prevalence on FTD is 15 to 22/100,000 individuals [124, 125]. *The most prevalent age is among 60–69 years old with roughly 13% having onset when younger than age 50. Heavy genetic loading for FTD is the main cause of younger onset, with up to half of cases being familial and up to 40% autosomal dominant in nature [99]. Survival partially depends on the variant of FTD and ranges from 2 to 3 years after symptom onset when motor neuron symptoms are prominent and up to 12 years for the semantic dementia variant [126].*

A new variant of FTD named phenocopy frontotemporal dementia (phFTD) has been described by Meijboom et al. recently [127]. It is an uncommon and poorly understood clinical syndrome characterized by similar clinical manifestations of BvFTD without abnormalities on MRI of the brain and without associated cognitive disorder. In contrast to phFTD, functional connectivity and white matter (WM) microstructural abnormalities have been observed in bvFTD. Some authors concluded that phFTD and bvFTD may belong to the same disease spectrum.

Canu et al. [128] reported some multiparametric MRI findings useful to differentiate early onset of AD (EOAD) from BvFTD based on the cortical thinning of the precuneus, posterior cingulate, superior and inferior parietal lobe, supramarginal, postcentral, and lingual gyri, and lateral occipital cortex bilaterally, and the left rostral and caudal middle frontal gyri seen in EOAD. Compared with the control group, the authors found a widespread pattern of cortical thinning involving all cerebral lobes, and compared to EOAD, BvFTD patients showed cortical thinning on the lateral orbitofrontal gyrus and temporal pole bilaterally, right entorhinal cortex, and right medial orbitofrontal gyrus. A severe cortical involvement is suggestive of EOAD, while a prominent white matter damage might be indicative of bvFTD.

7. Wernicke-Korsakoff syndrome and alcohol-related dementia

Wernicke encephalopathy and Korsakoff syndrome [Wernicke-Korsakoff syndrome (WKS)] and alcohol-related dementia (ARD) are preventable, life-threatening neuropsychiatric syndromes resulting from thiamine deficiency mainly in patients with chronic alcoholism, anorexia nervosa or patients who have undergone bariatric surgery for obesity, chronic hepatic disease, immunodeficiency syndromes, nutritional deficiencies of any cause, metastatic carcinomas, hyperthyroidism, prolonged parenteral nutrition, hyperemesis gravidarum, long-term dialysis and diuretic therapy, among other causes, and clinically, patients' complaints about short-term memory, confusional states, and neuropsychiatry manifestations.

In most of our patients, WKS is an acute nutritional disorder characterized by the clinical triad of ophthalmoplegia, cerebellar disorder, and altered mental state secondary to neuronal loss and hemorrhagic lesions in the periaqueductal gray matter of the midbrain, the anterior thalamus, and hypothalamus.

Altered mental state includes abulia, inattentiveness, and progressive memory disturbance with progressive deterioration of level of consciousness until comatose state if no treatment is received.

Before ophthalmoplegia is established, the eye movement abnormalities begin with limitations of abduction or horizontal gaze, and gait ataxia progresses to inability to stand.

All patients presenting thiamine deficiency improve their symptoms rapidly when thiamine is replaced in a timely fashion. Sometimes, patients do not improve completely, and nystagmus, broad-based gait, and cognitive dysfunction including a selective amnesic disorder (Korsakoff syndrome) remain present.

Some authors said that during the acute symptomatic stage of Wernicke encephalopathy, there is an impairment of the glucose and oxidative cellular energy metabolism, leading to an imbalance of the ionic gradients across the cell membrane causing cytotoxic edema (intracellular water shift and cell injury) and vasogenic edema because of breakdown of the blood-brain barrier permeability with intravascular fluids penetrating into cerebral parenchymal [102]. Currently, it is well known that the MRI findings of cytotoxic or vasogenic edema are a remarkable information to detect WE in clinical settings and the presence of bilateral

symmetrical signal hyperintensities in the periventricular region of the third ventricle, periaqueductal area, and hypothalamus confirms clinical impressions of WE [129, 130].

Dry beriberi happens when thiamine (vitamin B1) deficiency affects the central and peripheral nervous system, and wet beriberi happens when it damages the cardiovascular system. Ophthalmoplegia and nystagmus are present in 85% of patients with dry beriberi [131].

In developing countries, Wernicke syndrome is more likely to occur in nutritionally deficient alcoholics than in comparably deficient nonalcoholics, and thiamine deficiency in a nonalcoholic is more likely to produce wet beriberi with polyneuropathy than Wernicke syndrome [132]. However, several of Korsakoff's original patients had not been heavy drinkers [133].

Neuropathological report and MRI studies have confirmed that excessive and prolonged use of alcohol may lead to structural and functional damage that is permanent in nature [134].

Chronic and excessive drinking of alcohol can affect mentation in a different way, the commonest affected mechanism are systems of neurotransmitter by inhibition of excitatory glutamate receptors and by inhibition of γ -aminobutyric acid receptors [135]. In conclusion, alcohol intoxication has some mechanism to produce nervous system damage, including glutamate excitotoxicity and oxidative stress, which is increased by thiamine deficiency, hyperhomocysteinemia, and folate deficiency. Homocysteine functions as an agonist at glutamate NMDA receptors, increasing NMDA receptor transmission and the potential for excitotoxicity [136–138].

By neuropsychological investigations, Goldstein and Shelly [139] documented brain pathology in about 78% of patients with chronic alcoholism. However, there is debate about the relative contributions of the direct toxic effect of alcohol (ARD), and the impact of thiamine deficiency, to lasting damage [140]. The two main syndromes about alcohol-associated cognitive disorders are WKS and ARD. The last one has enjoyed little recognition as a discrete clinical entity because of lack of a distinct pathophysiological profile [141, 142].

Currently, it is well known that low-to-moderate ethanol consumption can reduce the risk of coronary syndrome and ischemic stroke due to the inhibitory effect of alcohol on platelet aggregation and the reduction of inflammatory markers and also by changing the lipid profile [143], while attempts to define a safe dose threshold for ethanol have been inconsistent. Parson and Nixon [144] reviewed 19 published studies addressing this issue and concluded that 5 or 6 "standard drinks" per day over extended periods resulted in "cognitive inefficiencies", that 7–9 drinks per day resulted in "mild cognitive deficits," and that 10 or more drinks per day caused impaired cognition of a degree encountered in frank alcoholics.

The neurotoxic effect of ethanol on memory and learning has been confirmed in animal studies [145, 146], and the abnormalities are found on the dentate granule cells, loss of hippocampal CA1 and CA3 pyramidal neurons, mossy fiber-CA3 synapses, pathological changes in neurons of cerebral cortex, hypothalamus, brainstem, loss of cholinergic neurons in the basal forebrain, and impaired pruning of redundant cortical synapses during early development [147–152].

Much of the debate surrounding ARD encompasses whether it is possible to have a dementia that is the direct result of ethanol neurotoxicity—a primary alcoholic dementia—or whether the clinical presentation of dementia represents another underlying pathology (that

is, thiamine deficiency) or multiple factors (for example, neurotoxicity in combination with nutritional deficiencies). Attempts to clarify this have been hindered by confounding factors that often accompany the lifestyles of alcohol abusers, such as head injury, psychiatric and other substance abuse comorbidities, and a higher rate of vascular risk factors [153].

According to neuroimaging and neuropathological findings, the main damage on the brain (in ethanol abuser) is prominent white matter loss (most remarkable in the prefrontal cortex, corpus callosum, and cerebellum) and neuronal loss in the hypothalamus, superior frontal association cortex, and cerebellum [154]. Nevertheless, the most susceptible region is the frontal lobe with documented evidence of markedly decreased neuron density, volume shrinkage, and abnormal glucose metabolism and perfusion [155]. Cholinergic neurotransmission in the basal forebrain, which plays a key role in attention, learning, and memory, also appears to be damaged by prolonged ethanol intake [156, 157].

Thiamine deficiency as a main cause for the development of ARD is another hypothesis, and ethanol abusers are at particularly high risk of thiamine deficiency due to poor dietary nutrition and also because of the direct effect of ethanol on thiamine metabolism [130].

Apart from deficient in thiamine, nicotinic acid, other B vitamins, and folate, alcoholics frequently develop neurological disorders associated with malnutrition, including cerebellar degeneration, amblyopia, polyneuropathy, and disorders affecting cognition. In pellagra, nicotinic acid deficiency results in skin, gastrointestinal, and mental abnormalities, which can progress to memory impairment, delusions, hallucinations, dementia, or delirium; hypertonus and startle myoclonus may be present. Symptoms usually improve following treatment with nicotinic acid or nicotinamide [158].

Some authors documented that ARD and WKS are different pathological process with overlapping clinical symptoms and both can be associated with ataxia and polyneuropathies [159].

One of the problems that we afford is the variety of available definitions for “standard drink” and its different meanings from country to country. While a standard drink in the United Kingdom contains 8 g of alcohol, a standard drink in Australia contains 10 g and in America and Japan contains 14 and 19.7 g, respectively [160], which affect the best comprehension of the information delivered in the medical literature.

As it was mentioned before, in the review made by Parson and Nixon in 1989, they found that consumption of five to six drinks per day (which, by US standards, equates to 70–84 g) over extended periods results in “cognitive inefficiencies,” while consumption of 10 or more standard drinks a day manifests as moderate cognitive deficits equivalent to that found in individuals with diagnosed alcoholism [144], and studies conducted by Oslin and colleagues [161] suggested that consuming 35 standard drinks a week for men and 28 for women for 5-year history constitutes a sufficient level of neurotoxic burden to risk the development of ARD. However, other studies found that light to moderate ethanol intake *reduced* the likelihood of dementia [162–170].

Damage of the brain seen on MRI is the biggest in female’s alcoholic patients compared with the male’s ones. Therefore, it seems to be that females are more susceptible than males to adverse ethanol’s effect, but their recovery after abstinence is better [171].

Because of the introduction of thiamine supplementation programs in some countries, as well as general dietary habits, there is no direct correlation between the prevalence of WE and per capita consumption of standard drinks, but all patients under suspicion of having WE should be treated immediately with parenteral thiamine [130]. Thiamine given orally does not work because it reaches poor concentration in plasma; therefore, a dosage of 200 mg IV three times a day (1 g may be required in the first 24 hours) for 5–7 days followed by oral thiamine in doses of 100 mg eight hourly for 1–2 weeks is strongly recommended. At this point, it is very important to highlight that other electrolyte deficiencies such as magnesium and niacin should also be corrected. Apart from parenteral thiamine, to eat food with a high content of vitamins such as peas, lentils, brown rice, pork, organ meats, milk, eggs, nuts, fruits, and vegetables is suggested. Alcohol interferes with thiamine uptake [172]. This treatment should be continued until no further improvement in signs and symptoms is evident [173].

Some patients with ARD and WKS have shown cognitive improvement following treatment with memantine, although these findings require replication [174, 175].

As we also mentioned before, ARD and WKS have some similarities. However, some neuropsychological studies have largely attempted to differentiate these syndromes by limiting individuals with more global cognitive impairment from WKS investigations and by excluding individuals with past symptoms of WKS from ARD studies, but the validity of this distinction is now being brought into question [140].

Ethanol concentration in blood raises blood levels of high-density lipoprotein cholesterol (HDL-C) in a dose-dependent fashion, and some studies suggest that this effect accounts for at least half of the protection against CAD [176]. Ethanol also increases insulin sensitivity [177], prevents platelet aggregation [178], increases fibrinolysis [179], opposes thrombin activity [180], and reduces inflammatory markers such as plasma C-reactive protein and fibrinogen levels [181].

While “dementia” in current neurological settings is typically used to describe a progressive disease of the brain, it perhaps more accurately encompasses a deterioration of intellectual or cognitive function that may or may not be progressive in nature [182]. Effect of ethanol on patients presenting ARD can be reversed if the diagnosis is made early enough (48–72 hours of the onset of symptoms) and adequately treated with parenteral thiamine [172]. Abovementioned foods are essential to replace the deficient vitamins/minerals, and faster recovery is usually seen in females than males as it was mentioned before as well. Support of family and friends is paramount in achieving abstinence [183]. The Wernicke’s encephalopathy and WKS also may be reversed if diagnoses made at early stage (48–72 hours of the onset of symptoms) and adequately treated with parenteral thiamine [143]. In WE, if the administration of right doses of thiamine IV is not reached, then the mortality rate will be elevated up to 20% level [184] or patient will continue progressing up to Korsakoff syndrome or ARD.

In a prospective 12-week study done by Cheon et al. on patients with probable ARD, they found that memantine (a low-affinity NMDA receptor antagonist) improved global cognition, quality of life, and behavioral symptoms on their patients [174]. Another investigation reported that rivastigmine at the dose of 3–12 mg per day for 2 months improved clinical manifestations of ARD [185].

Because not all ARD patients recover from abstinence, around 20% of them need long-term admissions and the amount of ARD patients will increase gradually due to the growing proportion of aging population and rise in per capita ethanol consumption [174, 183].

Physicians should be aware of preventable vitamin deficiency-related neuropsychiatric syndromes and should consider new signs and symptoms in patients with known psychiatric disorders as potential harbingers of reversible WE and irreversible WKS [185, 186]. Indirectly, ethanol abuse can cause intoxication, brain injury, withdrawal, hypoglycemia, chronic liver disease, Marchiafava-Bignami disease, and cognitive disorders, and nutritional deficit causes WKS and pellagra.

Marchiafava-Bignami disease, a rare disorder nearly always diagnosed in alcoholics, causes mania, depression, paranoia, and dementia, plus seizures, paresis, and ataxia and often progresses to coma and death within a few months; symptoms are not readily explained by the prominent corpus callosum demyelination that is the pathological hallmark of this poorly understood disease [187]. For the other hand, low dosage decreases the risk for dementia and AD is included [156].

Results of neuroimaging studies have corroborated postmortem neuropathological studies and have expanded the understanding of the neuropsychological deficits resulting from thiamine deficiency, alcohol neurotoxicity, and their combined effect [188].

8. Brief information about how to diagnose dementia

First of all, it is very important to highlight the importance of clinical assessment on any type of dementia followed by imaging and other investigations. The best assessment can be done by the well-skilled health-care professional knowing the clinical features of all dementia, duration, frequency, and rate of progression. This professional must guarantee an adequate comfortableness of the patients, while the process of diagnosis is finished. Therefore, the patient's fears regarding type of dementia and condition should be well managed including a full review of the patient's health care, family history and treatment history, proper evaluation for depression, toxic substance abuse and nutrition, and other conditions that can cause memory dysfunction such as infections, chronic anemia, vitamin deficiency, diabetes mellitus type 2, chronic kidney or liver disease, thyroid gland disease, cardiopulmonary disorders, and other risk factors for dementia including hearing loss. Currently, there is no single test that confirms Alzheimer's disease, although to achieve 90% accuracy is certain. Nevertheless, to identify the true underlying cause of the problem can be very difficult.

Findings from physical examination are crucial, and some laboratory tests such as CFS levels of total tau protein results are of relevant importance for identifying type of dementia and way of management. One of the most recent investigations has documented the results from evaluation of cerebrospinal fluid phosphorylated tau231 as a biomarker in the differential diagnosis of Alzheimer's disease and vascular dementia by assessing whether the use of sensitive and specific biomarkers such as phosphorylated tau proteins could contribute to an earlier and more accurate diagnosis of AD and VD, as well as to their differentiation, and the authors found that FS (p-tau231 and MMSE) has a strong potential to provide an early distinction between AD and VD [189, 190].

Obviously, according to the statement mentioned before, not every health professional is familiar with the complexities of dementia diagnosis. Therefore, to select the medical doctor with the necessary skill and experience to diagnose all different types of dementia is mandatory.

Below, we describe the most commonly used tests to diagnose dementia.

The MMSE is the most widely used cognitive screening test worldwide, and it is a very brief investigation of the patient's cognitive status used in diagnosing dementia types and serves to evaluate appearance and behavior, attitude, perception, orientation, judgment, cognition, abstraction, and insight. It can be administered quickly and repetitively. Patient is requested to identify the time, date, and place (including street, city, and state) where the test is taking place, be able to count backward, identify objects previously known by them, be able to repeat common phrases, perform basic skills involving math, language, and comprehension, and demonstrate basic motor skills. This examination provides information to distinguish organic from "functional" illnesses and also provides objective data regarding the patient's improving or deteriorating sensorium. It helps substantiate clinical decisions on competence, potential for danger, and hospitalization [191].

Some researchers have questioned the utility of brief cognitive tests such as the MMSE and the Montreal Cognitive Assessment in serial administration and suggested that brief cognitive tests may not accurately track changes in global cognition and other investigator also confirmed that there is limited utility in brief cognitive tests for tracking cognitive decline. Instead, they should be used for identifying participants who remain cognitively stable on follow-up. These results accentuate the importance of acknowledging the limitations of brief cognitive tests when assessing cognitive change [192]. Eleven versions of the MMSE were identified, and the Bertolucci et al. [193] version is the most cited in the medical literature [194].

The Mini-Cog is a brief, cognitive screening test that is frequently used to evaluate cognition in older adults in various settings; the mini-cog takes only a few minutes to administer and is used as an initial screening for different types of cognitive disorders. The patient is required to identify three objects in the office, then draw the face of a clock in its entirety from memory, and finally, recall the three items identified earlier.

There are currently few studies assessing the diagnostic test accuracy of the Mini-Cog in community settings. The limited number of studies and the methodological limitations that are present in the study done by Fage et al. *made it difficult to provide recommendations for or against the use of the Mini-Cog as a cognitive screening test in community settings. Additional well-designed studies comparing the Mini-Cog to other brief cognitive screening tests are required in order to determine the accuracy and utility of the Mini-Cog in community-based settings [195].* The clock drawing test and the MMSE have been used in dementia screening over the past 30 years, and they were the tests of choice in almost all relevant investigations on cognitive disorders already done.

Montreal Cognitive Assessment (MoCA) is a cognitive screening instrument that was designed to address some of the limitations of the MMSE [196].

Based on the MoCA scores, the patients were further categorized as normal cognition (PD-NC) if their MoCA scores were 26–30 or mild cognitive impairment (PD-MCI) if their scores were 18–25 according to a Malaysian study [197].

Some authors discovered that the Parkinson's disease-cognitive rating scale (PDCRS) was better than MoCA in detecting MCI, while other test was more specific for executive dysfunction.

They failed to demonstrate the association between plasma α -synuclein levels and cognitive impairment in their PD patients. However, genotype *e3/e4* and being a carrier of *e4* allele of the *ApoE* gene correlated with the presence of executive dysfunction in PD patients. Therefore, these findings can bring new perspectives to the understanding of the genetic influence on cognitive impairment and confirm a possible link between *ApoE* and cognitive impairment in PD [198].

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Conflict of interest

The authors declare that this chapter was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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