https://doi.org/10.22364/lmahc.fd.24.02

Diagnostic Challenges of Alzheimer's Disease in Clinical Practice

Zanda Priede, Sintija Strautmane
Rīga Stradiņš University

Alzheimer's disease (AD) is the most common form of dementia. Together with other dementias, it is the 7th leading cause of death worldwide. AD is a chronic, neurodegenerative disorder, usually affecting people after the age of 65. There are no pathognomonic signs, furthermore, the beginning of AD is very insidious. Most frequently, AD starts with memory impairment, speech difficulties, difficulties to orientate oneself in space, changes in patient's behaviour and personality, which result in patient becoming bedridden. Diagnostics is still challenging, however, with development of technologies, there is a hope to diagnose the disorder as soon as possible to provide optimal quality of life for the patient.

Keywords: Alzheimer's disease, neurodegenerative disorder, memory, behaviour

Introduction

According to the World Health Organization, global population life expectancy has increased by more than 6 years. When comparing population life expectancy in 2000 with 2019, it is found that the average population life expectancy in the world in 2000 was 66.8 years, while in 2019 the average population survival in the world reached 73.4 years. Quality of life and health status also play an important role when it comes to life expectancy. Life expectancy with good health and subsequent optimal quality of life has increased by 8%, i.e. from 58.3 years in 2000 to 63.7 years in 2019. These data are more associated with a reduction in mortality than with a reduction in the number of years spent living with a disability. Consequently, the increase in survival for people in good health (5.4 years) still lags behind the increase in overall life expectancy (6.6 years) [1].

Global changes in population age demographics and the subsequent expected increase in age-related diseases indicate a serious public health problem. In the elderly population, multimorbidity is more common, which includes, for example, arterial hypertension, atherosclerosis, diabetes mellitus, heart rhythm disturbances, heart failure, lung diseases, thromboses, cerebral infarctions, oncological diseases and other diseases, including dementia [2].

According to the guidelines published by the European Federation of Neurological Associations in 2012, which promote the diagnosis and management of dementia-related diseases, dementia is defined as a brain disorder that causes permanent and versatile cognitive impairment, including impairment of memory, language, visual spatial sensations, various skills, causal understanding and reasoning abilities. These cognitive changes culminate in personality and behaviour changes of varying intensity, negatively impacting the individual in their daily activities, limiting them in comparison with the previous period of life. Therefore, early recognition of dementia symptoms is very important to delay the development of dementia and correct the course of the disease, which would be realized in the best possible quality of life [3].

It is currently known that dementia affects 5.4% of people over the age of 65, in addition, its prevalence increases with age to 20–25%, and even more at the age of 85 [4, 5]. Alzheimer's disease and other dementias are the most common cause of disability later in life and dementia is currently the 7th leading cause of death [6, 7]. According to statistics on the prevalence of Alzheimer's disease in the world today, about 50 million people have Alzheimer's disease or related dementia, and in addition, only one in four of the population has a proven and diagnosed Alzheimer's disease [6]. Alzheimer's disease is now more common in Western Europe, with 14 million Europeans expected to develop dementia by 2030 [3].

Neurodegenerative diseases are defined as a group of heterogeneous diseases characterized by progressive diseases of the central nervous system. Their origin can be related not only to heredity, but also to sporadic cases that develop when structural changes occur in the cells of the nervous system, or neurons, resulting in abnormal cellular function or even loss of cellular functions. Abnormal protein products precipitate, triggering the mechanism of neuronal death.

1. Definition of Alzheimer's disease

As established above, dementia is a general term for persistent and multifaceted cognitive impairment, which includes Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia. Consequently, this term is non-specific [3].

In turn, Alzheimer's disease is defined as a chronic neurodegenerative disease, the characteristic histological picture of which includes two typical findings:

1) extracellular aggregates of the beta-amyloid protein, which cause an inflammatory reaction, progressive oxidative damage to nerve cells or neurons and their synapses, and subsequent neuronal death, which gradually leads to brain atrophy;
2) intraneuronal platelets of phosphorylated tau protein, the structure of which is altered, and when these platelets bind to other tau proteins, the cell transport

system is damaged, causing inter-neuronal signal transmission disorders and inevitable neuronal death [8, 9, 10].

Despite these two typical histological findings, patients with Alzheimer's disease are additionally characterized by a selective loss of neurons and their interconnections, or synapses, as well as an increased number of astrocytes (glial cells) and their activity, acetylcholine deficiency, as well as dysfunction or even atrophy of the limbic system structures [11, 12].

As a result of Alzheimer's disease, patients develop cognitive deficits, which hamper the performance of even the most basic everyday tasks; the patients become fully dependent on care, incurring a burden on caregivers and significantly increasing health care costs. This disease leads to the premature death of the affected individual – the projected survival is on average 10 years from the time of diagnosis [11].

Alzheimer's disease is the most common form of dementia, accounting for up to 75% of all moderate forms of cognitive impairment on its own or in combination with other cognitive disorders [10]. The disease usually starts after the age of 65, and its incidence doubles every five years, but it is not part of normal aging [10, 11]. It should be noted that age is the primary and main risk factor for the development of Alzheimer's disease. Interestingly, gender also plays a role in the development of Alzheimer's disease – in women, this risk is higher due to hormonal differences from men, different contact with environmental agents during life, as well as different lengths of education. However, these are not the main risk factors. No less important is a positive family history of first-degree relatives, chromosome 21 trisomy (Down syndrome), including specific mutations in chromosomes 14 and 1, low level of education, low educational and career achievement, social isolation, insufficient physical activity, prolonged psycho-emotional stress, diabetes mellitus and impaired glucose tolerance, as well as small head size and brain volume; presenilin mutation and altered APP gene, apolipoprotein E-e4 allele, head injury. Possible risk factors include lifestyle factors such as smoking, excessive use of alcohol and other intoxicating substances, exposure to industrial solvents and pesticides, as well as exposure to electromagnetic fields, increased maternal age, cerebrovascular disease, cardiovascular disease and thyroid dysfunction [11].

2. Chameleons in the clinical picture of Alzheimer's disease

As indicated above, age is a major risk factor in the development of Alzheimer's disease. Unfortunately, there are no clinical symptoms of pathognomies, i.e. no symptoms that specifically indicate Alzheimer's disease. Similar to other forms of dementia, the onset of Alzheimer's disease is slow, non-specific and sometimes does not even raise suspicion of the disease.

Initially, the medial temporal cortex and associative fields are affected pathologically. The process then spreads to the frontal and parietal cortex. Consequently, temporary memory impairment develops (the brain structure involved is the hippocampus), but due to memory impairment and aphasia (the brain structure involved is the pre-Silvian groove region) – orientation disorders, visual spatial dysfunction (the brain structure involved is the cortex of the parietal lobe) and executive function deficiency (the brain structure involved is the cortex of the frontal lobe) [13].

Thus, Alzheimer's disease starts with memory problems. The patient begins to forget recently learned information or events. It is believed that such manifestations have occurred in all people, regardless of age, so additional examination is not always necessary. However, in the event that the deterioration of memory (quick forgetting, repetition of previously asked questions or something that was previously said, loss of objects, inattention, placement of objects in places not normally suitable for them) progresses obviously, and if the patient increasingly forgets recent events, one should start to think [11, 14].

In connection with memory impairment, difficulties in expressing oneself also appear. Patients begin to have a difficulty to find words in sentences, make pauses; patients can replace the required words with a wrong word or substitute a more complex word with a simpler one. Often family members automatically replace the missing words in the conversation themselves. Other serious illnesses, such as cerebral infarction affecting the Brock area of the left hemisphere of the brain, which is directly related to the provision of normal language function, may also have similar symptoms [11, 14].

The visual spatial sense of a patient is affected, for example, they may become confused in previously familiar and safe places, even get lost in them; it may be difficult to memorize a new route. Again, there is a differential diagnosis between ischemic brain injury in the posterior vascular area. In patients with Alzheimer's disease, when the frontal cortex is affected, its dysfunction also appears [11, 14].

As the disease progresses, the behavioural disorders gradually worsen – the patient may be emotionally labile, crying, become quickly irritable and even aggressive; he may be negative and uncritical, unable to adequately respond to various situations and make the right decisions, he may have difficulties in performing everyday duties. Hence, personality changes may also appear. The patient may become apathetic, have depression, anxiety, irritability, suffer from nightmares, for example, that strangers have entered home, etc. In such a situation, Alzheimer's disease should be differentiated from psychiatric diseases, for example, schizophrenia, bipolar disorder, depression with manic episodes, etc. In this case, differential diagnosis helps, distinguishing between psychiatric diseases and cerebrovascular processes in the brain, for example, in connection with thalamus circulation disorders. Atrophy and/or dysfunction of limbic system

structures reduces patients' ability to deal with their emotions, including fear and anxiety. As a result, the patient is under heightened stress and experiences an increased release of the stress hormone cortisol; as its level rises, hippocampal atrophy may develop [11, 14].

Gradually, the patients diagnosed with Alzheimer's disease continue to lose their ability to function until they become fully care-dependent on a 24-hour basis, usually in long-term care facilities [11]. At this stage, they also have serious self-care difficulties (such as difficulty eating, bathing, using the toilet, etc.), using everyday items (doing chores, cooking, using the phone, etc.). Being aware that in this case patients are not capable to be critical of themselves, it is very important to build and achieve mutual trust with the patient's relatives in a timely manner and to collect detailed medical history data about the patient [11].

In some cases, Alzheimer's patients may also have an atypical or unusual clinical picture, that is, they do not have a progressive amnestic dementia. Then diagnosing Alzheimer's is even more of a challenge. In such patients, atypical neuroanatomy and, above all, neurofibrillary meshes are observed in neuropathological examinations, which is associated with the most pronounced clinical picture. It has been concluded that such changes are more common in patients with Alzheimer's disease at an early age (persons under the age of 65), and this fact is the subject of current discussion [15, 16].

In persons with an atypical clinical picture of Alzheimer's disease, the first symptoms may be associated with a deterioration of vision called posterior cortical atrophy syndrome. Initially, these patients often see an ophthalmologist, for example, with complaints about spatial perception disorders, simultaneous agnosia, oculomotor apraxia, homonymous visual field disorders, apperceptive prosopagnosia, inability to differentiate right from left, difficulties in performing bimanual tasks, such as dressing, etc., but memory and speech disorders in this case are not pronounced [17].

In turn, primary progressive aphasia is attributed to a group of clinical and pathophysiological heterogeneous neurodegenerative diseases, which are characterized by progressive language disorders with relatively preserved memory and other cognitive functions. This is one of the atypical clinical variants of Alzheimer's disease [18].

Among Alzheimer's patients, one of the first symptoms may be executive dysfunction, which is basically related to damage to the frontal lobe of the brain. In this case, brain atrophy occurs in the frontotemporal cortical regions. In addition, a faster progression of the disease is also observed in such patients with an atypical clinical picture compared to patients with a typical clinical picture of Alzheimer's disease with memory impairment [19].

Alzheimer's disease may be associated with other processes, such as vascular damage, including vascular dementia, Lewy Body Dementia, and Parkinson's disease. Such combinations may affect the patient's clinical picture and pose even

greater diagnostic and treatment challenges even for experienced professionals, however, according to literature, the most common combination for Alzheimer's disease is with vascular dementia [20].

3. Diagnostic challenges in Alzheimer's disease

Alzheimer's disease should be thought of when it comes to an elderly patient with progressive memory impairment, as well as manifestations of the disorder in at least one other cognitive domain, which negatively affects the patient's daily life.

As with any disease, the first step in Alzheimer's disease is to carefully collect the patient's medical history. Knowledge of the loss of the patient's physical and mental abilities, as well as their difficulties in everyday life, is one of the ways to establish, as soon as possible, whether and how well the patient's (independent) functioning abilities have been preserved [11, 12]. Most often, such medical history data is collected by interviewing the patient's family members.

The initial tool to use in direct communication with the patient is the Montreal Cognitive Impairment Assessment Scale (MoCA; norm: at least 26 points out of 30). This test is quick, short and simple, and when compared to other tests, such as the Mini-Mental State Examination, it has a higher sensitivity for determining executive function and language disorders. However, it should be noted that the diagnosis of dementia, including Alzheimer's disease, cannot be based solely on the evaluation of these tests. The collection of detailed medical history data on the patient is much more important [21].

A number of criteria for differential diagnosis in Alzheimer's disease have also been developed. Two sources are most commonly used for this purpose: The Diagnostic and Statistical Manual of Mental Disorders, and the criteria developed by the National Institute on Aging – Alzheimer's Association. Criteria for diagnosing Alzheimer's disease have been developed in each of these sources [3].

Neuropsychological testing may also be useful in assessing disease dynamics in patients with dementia and cognitive impairment. These tests, for example, help to determine the patient's baseline condition in order to follow the clinical picture and the patient's daily functioning in the future and to help differentiate different forms of neurodegenerative dementia from cognitive impairment of other aetiologies. They are used to find the actual level of functioning of the patient, to make appropriate recommendations, for example, when assessing the patient's ability to drive a vehicle, make financial decisions, etc., as well as to determine the compensatory mechanisms of the patient.

In addition to the above, if a patient is suspected of having Alzheimer's disease, imaging should be performed, primarily – magnetic resonance imaging (MRI) of the brain. This test also plays an important role in the differential diagnosis, which allows to exclude other diseases, including cerebrovascular diseases and structural

changes in the brain, such as chronic subdural hematoma, brain tumour, normal pressure hydrocephalus, regional brain atrophy, or frontotemporal dementia and other neurodegenerative diseases [22].

Structural changes in the brain in patients with Alzheimer's disease, which the MRI can identify, include both generalized and focal atrophy, as well as damage to the brain's white matter, but in general these changes are non-specific. The most characteristic focal finding in patients with Alzheimer's disease is reduced hypothalamic volume and/or atrophy of the medial temporal lobes [23]. The decrease in hypothalamic volume is also a normal part of aging, so age-specific criteria are necessary in this case. Correlation of MRI findings with the patient's clinical picture is essential. Separate studies indicate that MRI findings may be useful in predicting deterioration in the functional status of Alzheimer's patients. Hippocampal volumetry using age-adjusted norms may aid in predicting the progression of mild cognitive deficits in dementia, however, these tools are currently not widely used, and the results obtained have not yet been validated in everyday clinical practice [24].

Functional brain imaging with 18-F fluorodeoxyglucose positron emission tomography (FDG-PET) or single proton emission computed tomography (SPECT) demonstrates different regions of the brain with hypometabolism (PET) and hypoperfusion (SPECT) in patients with Alzheimer's disease. These regions include the hippocampus, medial parietal lobes, lateral parietal and posterior temporal map [25]. It is important to mention that in practice FDG-PET may be the most useful test to differentiate and distinguish between Alzheimer's disease and frontotemporal dementia in patients with an atypical clinical picture, as well as to distinguish between neurodegenerative conditions such as depression. FDG-PET and SPECT are the only neuroradiological examination methods that are currently quite widely available in the world in daily clinical work.

Additionally, amyloid positron emission tomography (PET) imaging is possible by measuring the amount of amyloid in the brain. The examination is carried out in order to identify Alzheimer's disease in a targeted manner and to distinguish it from other causes of dementia [26]. At present, it is possible to perform amyloid PET imaging, so research is actively being conducted to search for markers appropriate for Alzheimer's disease tau proteinopathy, so that tau PET imaging can also be performed [27].

A novelty in the diagnosis of Alzheimer's disease patients are biomarkers. Based on data from the literature, there are currently some extensively studied biomarkers for the molecular and degenerative tracking process of Alzheimer's disease patients, which may be supportive in the diagnosis of the disease, but are not yet fully recommended in everyday clinical diagnostic practice. This testing helps to obtain additional confirmation in the diagnosis of Alzheimer's disease, and the results may be useful in a variety of other situations, such as for patients with early-onset dementia or an atypical clinical picture of Alzheimer's disease, in

which the differential diagnosis also includes other non-amyloid neurodegenerative diseases, such as frontotemporal dementia [28].

Potential biomarkers include beta-amyloid deposition markers in the brain, so it is recommended to use only one specific marker when testing dementia patients under the age of 66. For example, low levels of cerebrospinal fluid or fluid beta-amyloid-42 support the diagnosis of Alzheimer's disease – elevated levels of a marker in amyloid PET images. Potential biomarkers also include neurodegeneration markers. For example, an increased tau protein in cerebrospinal fluid or cerebrospinal fluid (total or phosphorylated) supports the diagnosis of Alzheimer's disease – decreased metabolism of fluorodeoxyglucose in temporal and parietal cortex pet; temporal lobe (medial, basal and lateral) and parietal lobe medial cortical atrophy MRI. Regardless of whether clinical criteria for probable Alzheimer's disease are obtained: if both markers (beta-amyloid and neurodegeneration markers) are negative, then there is a low probability that dementia is associated with Alzheimer's disease pathology [9, 14, 29].

In general, topographic biomarkers are less specific than molecular biomarkers, but have a better correlation with the patient's clinical picture. Today, research on biomarkers continues actively, trying to include them in the definition of Alzheimer's disease in order to provide not only a clinical diagnosis, but also a biological basis for the diagnosis of Alzheimer's disease. In addition, neurodegeneration markers also provide information about the degree of the disease. Plasma biomarkers are not yet proven to play a role in clinical practice, so further research is needed in this area [30].

Although research on biomarkers is currently active, there is still a lack of optimized biomarkers. This limits the diagnosis, progression and treatment evaluation of the disease. Validated, minimally invasive biomarkers could detect the causes of dementia as soon as possible, allowing early and appropriate therapy in patients with dementia. Consequently, it would be possible to avoid treating neurodegenerative diseases with the same medications, which, logically, do not provide improvement. Increased use of biomarkers would open the door to much-needed personalized medicine [31, 32].

It should be noted that routine blood tests do not show indications specific to Alzheimer's disease, so they do not play such a big role in diagnostics. There is also the possibility of genetic testing, but it is usually not recommended for routine evaluation in patients with Alzheimer's disease. It is possible to detect specific mutations in chromosomes 21, 14 and 1 in patients suspected of having an early family form of Alzheimer's disease that is inherited by autosomal dominant individuals. It is known that approximately 50% of cases are caused by mutations in the APP, PSEN1 and PSEN2 genes [9]. Genetic testing is not recommended if there are asymptomatic family members in the family, and also if the patient has not been previously consulted by a geneticist [30].

Conclusions

Alzheimer's disease is the most common form of dementia, which in itself and/or in combination with other cognitive diseases places a serious burden on society. With advances in technology, it is now possible to diagnose Alzheimer's disease earlier, but in many cases, it still goes unnoticed, with only one in four cases confirmed. This chapter, therefore, emphasized not only the enormous socio-economic burden of Alzheimer's disease, but also described the variability of the clinical picture of the "chameleon type" disease, and outlined the challenges of diagnosing the disease in everyday clinical practice. At the same time, there is a hope that in the future the possibilities of diagnosing the disease at the earliest possible stage will be available in order to provide the patient with an optimal quality of living and the longest possible happy life.

REFERENCES

1. Vats P. P. Assessment of knowledge level of rural people of Uttarakhand regarding UHC (Universal health care) services. TPI International Journal. 2022; 11 (3): 739–743. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-life-expectancy-and-healthy-life-expectancy#:~:text=Globally%2C%20life%20expectancy%20has%20increased,reduced%20years%20lived%20with%20disability
2. Lippi G., Wong J., Henry B. M. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Polish Archives of Internal Medicine. 2020; Apr 30; 130 (4): 304–309. https://www.mp.pl/paim/issue/article/15272/ DOI: 10.20452/pamw.15272
3. Sorbi S., Hort J., Erkinjuntti T., Fladby T., Gainotti G., Gurvit H., Nacmias B., Pasquier F., Popescu B. O., Rektorová I., Religa D. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. European Journal of Neurology. 2012; Sep; 19 (9): 1159–1179. DOI: 10.1111/j.1468-1331.2012.03784.x
4. Hort J. O., O'Brien J. T., Gainotti G., Pirttila T., Popescu B. O., Rektorová I., Sorbi S., Scheltens P., EFNS Scientist Panel on Dementia. EFNS guidelines for the diagnosis and management of Alzheimer's disease. European Journal of Neurology. 2010; Oct; 17 (10): 1236–1248. DOI: 10.1111/j.1468-1331.2010.03040.x
5. Rizzi L., Rosset I., Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Research International. 2014; Oct; 2014: 908915. DOI: 10.1155/2014/908915
6. Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia. 2019; Mar; 15 (3): 321–387. https://www.alzheimers.net/alzheimers-statistics
7. Wortmann M. Dementia: A global health priority-highlights from an ADI and World Health Organization report. Alzheimer's Research & Therapy. 2012; Oct; 4 (5): 1–3. https://www.who.int/news-room/fact-sheets/detail/dementia DOI: 10.1186/alzrt143
8. Dharmarajan T. S., Gunturu S. G. Alzheimer's disease: a healthcare burden of epidemic proportion. American Health & Drug Benefits. 2009; Jan; 2 (1): 39.

9. Budson A. E., Solomon P. R. Memory Loss, Alzheimer's Disease, and Dementia. A Practical Guide for Clinicians. 2nd edition, Chapter 4. 2016; pp. 47–68. In: Kirshner H. S. Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians.
10. Lakhan S. E., Chawla J. Alzheimer Disease. Medscape Medical News. 2016; Aug 16. https://emedicine.medscape.com/article/1134817-overview?form=fpf
11. Fiest K. M., Roberts J. I., Maxwell C. J., Hogan D. B., Smith E. E., Frolkis A., Cohen A., Kirk A., Pearson D., Pringsheim T., Venegas-Torres A. The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. Canadian Journal of Neurological Sciences. 2016; Apr; 43 (S1): S51–82. DOI: 10.1017/cjn.2016.36
12. Breitve M. H., Hynninen M. J., Brønnick K., Chwiszczuk L. J., Auestad B. H., Aarsland D., Rongve A. A longitudinal study of anxiety and cognitive decline in dementia with Lewy bodies and Alzheimer's disease. Alzheimer's Research & Therapy. 2016; Dec; 8 (1): 1–6. DOI: 10.1186/s13195-016-0171-4
13. Park K. W., Kim H. S., Cheon S. M., Cha J. K., Kim S. H., Kim J. W. Dementia with Lewy Bodies versus Alzheimer's Disease and Parkinson's Disease Dementia: A Comparison of Cognitive Profiles. Journal of Clinical Neurology. 2011; Mar 1; 7 (1): 19–24. DOI: 10.3988/jcn.2011.7.1.19
14. Budson A. E., Solomon P. R. Memory Loss, Alzheimer's Disease, and Dementia. A Practical Guide for Clinicians. 2nd edition, Chapter 2. 2016; pp. 5–37. In: Kirshner H. s. Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians.
15. Galton C. J., Patterson K., Xuereb J. H., Hodges J. R. Atypical and Typical Presentations of Alzheimer's Disease: A Clinical, Neuropsychological, Neuroimaging and Pathological Study of 13 Cases. Brain. 2000; Mar 1; 123 (3): 484–498. DOI: 10.1093/brain/123.3.484
16. Alladi S., Xuereb J., Bak T., Nestor P., Knibb J., Patterson K., Hodges J. R. Focal cortical presentations of Alzheimer's disease. Brain. 2007; Oct 1; 130 (10): 2636–2645. DOI: 10.1093/brain/awm213
17. Crutch S. J., Schott J. M., Rabinovici G. D., Murray M., Snowden J. S., Van der Flier W. M., Dickerson B. C., Vandenberghe R., Ahmed S., Bak T. H., Boeve B. F. Consensus classification of posterior cortical atrophy. Alzheimer's & Dementia. 2017; Aug; 13 (8): 870–884. DOI: 10.1016/j.jalz.2017.01.014
18. Josephs K. A., Whitwell J. L., Duffy J. R., Vanvoorst W. A., Strand E. A., Hu W. T., Boeve B. F., Graff-Radford N. R., Parisi J. E., Knopman D. S., Dickson D. W. Progressive aphasia secondary to Alzheimer disease vs FTLD pathology. Neurology. 2008; Jan 1; 70 (1): 25–34. DOI: 10.1212/01.wnl.0000287073.12737.35
19. Blennerhassett R., Lillo P., Halliday G. M., Hodges J. R., Kril J. J. Distribution of pathology in frontal variant Alzheimer's disease. Journal of Alzheimer's Disease. 2014; Jan 1; 39 (1): 63–70. DOI: 10.3233/JAD-131241
20. Arvanitakis Z., Capuano A. W., Leurgans S. E., Bennett D. A., Schneider J. A. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. The Lancet Neurology. 2016; Aug 1; 15 (9): 934–943. DOI: 10.1016/S1474-4422(16)30029-1
21. Rossetti H. C., Lacritz L. H., Cullum C. M., Weiner M. F. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. Neurology. 2011; Sep 27; 77 (13): 1272–1275. DOI: 10.1212/WNL.0b013e318230208a

22. Knopman D. S., DeKosky S. T., Cummings J. L., Chui H., Corey–Bloom J., Relkin N., Small G. W., Miller B., Stevens J. C. Practice parameter: diagnosis of dementia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; May 8; 56 (9): 1143–1153. DOI: 10.1212/wnl.56.9.1143

23. Whitwell J. L., Dickson D. W., Murray M. E., Weigand S. D., Tosakulwong N., Senjem M. L., Knopman D. S., Boeve B. F., Parisi J. E., Petersen R. C., Jack Jr. C. R. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. The Lancet Neurology. 2012; Oct 1; 11 (10): 868–877. DOI: 10.1016/S1474-4422(12)70200-4

24. McEvoy L. K., Holland D., Hagler Jr. D. J, Fennema-Notestine C., Brewer J. B., Dale A. M. Mild cognitive impairment: baseline and longitudinal structural MR imaging measures improve predictive prognosis. Radiology. 2011; Jun; 259 (3): 834. DOI: 10.1148/radiol.11101975

25. Hu W. T., Wang Z., Lee V. Y., Trojanowski J. Q., Detre J. A., Grossman M. Distinct cerebral perfusion patterns in FTLD and AD. Neurology. 2010; Sep 7; 75 (10): 881–888. DOI: 10.1212/WNL.0b013e3181f11e35

26. Rabinovici G. D., Rosen H. J., Alkalay A., Kornak J., Furst A. J., Agarwal N., Mormino E. C., O'Neil J. P., Janabi M., Karydas A., Growdon M. E. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. Neurology. 2011; Dec 6; 77 (23): 2034–2042. DOI: 10.1212/WNL.0b013e31823b9c5e

27. Fleisher A. S., Pontecorvo M. J., Devous M. D., Lu M., Arora A. K., Truocchio S. P., Aldea P., Flitter M., Locascio T., Devine M., Siderowf A. Positron emission tomography imaging with [^{18}F]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. JAMA neurology. 2020; Jul 1; 77 (7): 829–839. DOI: 10.1001/jamaneurol.2020.0528

28. McKhann G. M., Knopman D. S., Chertkow H., Hyman B. T., Jack Jr. C. R., Kawas C. H., Klunk W. E., Koroshetz W. J., Manly J. J., Mayeux R., Mohs R. C. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia. 2011; May 1; 7 (3): 263–269. DOI: 10.1016/j.jalz.2011.03.005

29. Filippi M., Agosta F., Barkhof F., Dubois B., Fox N. C., Frisoni G. B., Jack C. R., Johannsen P., Miller B. L., Nestor P. J., Scheltens P. EFNS task force: the use of neuroimaging in the diagnosis of dementia. European Journal of Neurology. 2012; Dec; 19 (12): 1487–1501. DOI: 10.1111/j.1468-1331.2012.03859.x

30. Karikari T. K., Pascoal T. A., Ashton N. J., Janelidze S., Benedet A. L., Rodriguez J. L., Chamoun M., Savard M., Kang M. S., Therriault J., Schöll M. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. The Lancet Neurology. 2020; May 1; 19 (5): 422–433. DOI: 10.1016/S1474-4422(20)30071-5

31. Frisoni G. B., Boccardi M., Barkhof F., Blennow K., Cappa S., Chiotis K., Démonet J. F., Garibotto V., Giannakopoulos P., Gietl A., Hansson O. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. The Lancet Neurology. 2017; Aug 1; 16 (8): 661–676. DOI: 10.1016/S1474-4422(17)30159-X

32. Reitz C. Toward precision medicine in Alzheimer's disease. Annals of Translational Medicine. 2016; Mar; 4 (6): 107. DOI: 10.21037/atm.2016.03.05