

Epidemiology of Alzheimer's disease in the Odesa region

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The aim of the work was to study the epidemiology of Alzheimer's disease in the Odesa region.

Materials and methods. The study was carried out on the basis of the Regional Mental Health Center (Odesa) in 2016–2021. The data of the primary referral of patients with a verified diagnosis of Alzheimer's disease were analyzed. Statistical processing of the obtained data was performed by frequency analysis methods using standard MS Excel packages (Microsoft Inc., USA). The population of the Odesa region was determined according to the State Statistics Service of Ukraine.

Results. According to the retrospective analysis over the past 5 years, there was a constant increase in the number of identified patients with Alzheimer's disease, from 4.9 cases per 100,000 population in 2016 to 6.0 cases in 2020 with a slight predominance of women in the structure of cases. Brain MRI was performed only in 29 (4.6 %) patients, EEG in 41 (6.5 %) patients. There were no cases of familial Alzheimer's disease or early-onset Alzheimer's disease. In 2020, Alzheimer's and dementia deaths reached 14,196 or 2.54 % of total mortality in Ukraine.

Conclusions. The prevalence of Alzheimer's disease was 6.0 cases per 100,000 in the population of the Odesa region at the end of 2021, which was an order of magnitude less than the global average. The mean score on the MMSE scale was 18.6 ± 0.5 . The analysis on subscales has shown the prevalence of memory, spatial orientation and verbal disorders. The Ukrainian population is characterized by the small number of patients of the older age group (3.3 %) and the predominance of female patients (59.4 %).

Ключові слова:

хвороба Альцгеймера, епідеміологія, Україна, Одеська область.

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Епідеміологія хвороби Альцгеймера в Одеській області

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Мета роботи – вивчення епідеміології хвороби Альцгеймера в Одеській області.

Матеріали та методи. Дослідження здійснили на базі Обласного центру психічного здоров'я (м. Одеса) у 2016–2021 рр. Проаналізували дані первинного направлення пацієнтів із верифікованим діагнозом хвороба Альцгеймера. Статистичне опрацювання результатів здійснили із застосуванням методів частотного аналізу, використавши стандартні пакети MS Excel (Microsoft Inc., США). Кількість населення Одеської області визначили за даними Державної служби статистики України.

Результати. За результатами ретроспективного аналізу, протягом останніх 5 років відбувалося постійне зростання кількості встановлених діагнозів хвороба Альцгеймера: з 4,9 випадку на 100 тис. населення у 2016 році до 6,0 випадку у 2020 році. У структурі захворюваності на хворобу Альцгеймера виявили незначне переважання жінок. МРТ головного мозку виконали тільки 29 (4,6 %) хворим, EEG – 41 (6,5 %) пацієнтові. Випадки сімейної форми хвороби Альцгеймера та хвороби Альцгеймера з раннім початком не зафіксовані. У 2020 році в Україні померли 14 196 осіб від хвороби Альцгеймера та деменції – 2,54 % від загальної кількості смертей.

Висновки. Поширеність хвороби Альцгеймера серед населення Одеської області наприкінці 2021 року становила 6,0 випадку на 100 тис. населення; це істотно менше, ніж середній показник у світі. Середній бал за шкалою MMSE становив $18,6 \pm 0,5$. Аналіз за субшкалами показав переважання порушень пам'яті, просторової орієнтації та вербальних розладів. Для населення України характерна незначна кількість хворих старшої вікової групи (3,3 %) та переважання жінок (59,4 %).

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive and behavioral impairments, significantly affecting the possibilities of social and professional functioning. The disease is incurable, has a fairly long preclinical stage and is steadily progressing [1,2]. In Alzheimer's disease, pathological changes develop in the hippocampus, the structure responsible for encoding memories, and in other zones of the neocortex involved in thinking and decision-making processes [1–3].

Every tenth person over the age of 65 years in the world has signs of dementia, two-thirds of these cases are represented by AD. The fact that women predominate among patients with AD is most likely due to their longer life span [4,5].

There are no exact statistics on the AD prevalence in Ukraine. The frequency of deaths from AD in Ukraine is 0.3 per 100,000 people, while this figure is 112 per 100,000 people in the UK, the USA – 82, France – 76, Germany – 51 [5]. This indicates the underdiagnosis of AD in Ukraine.

Modern guidelines for the diagnosis and treatment of AD are largely focused on a strong resource base. At the same time, a routine use of magnetic resonance imaging (MRI) and other neuroimaging methods remains inaccessible to a significant number of medical institutions around the world. This makes it difficult to diagnose the early stages of the disease. In fact, a patient comes into the view of a physician with already manifested dementia [4,6,7].

But not only in developing countries, but also in developed ones, the diagnosis of AD is made mainly on the basis of a general clinical examination. Of course, the importance of additional diagnostic methods cannot be denied. The arrival of such methods as electroencephalography, MRI, positron emission tomography (PET), complex clinical and laboratory tests in the diagnostic arsenal greatly facilitates the search for causes of dementia [1,2,8]. This has led to the development of diagnostic criteria applicable in clinical research settings and also where the availability of additional neuroimaging and/or cerebrospinal fluid (CSF) analysis methods is limited [7,8].

Hippocampal atrophy is one of the most important biomarkers of AD [9]. Functional MRI can identify patients with minimal changes in the hippocampal structures, which makes it possible to distinguish patients with initial stages of AD from apparently healthy individuals [10]. Visualization of default mode networks (DMN) also allows distinguishing between AD and vascular dementias. This method may complement PET scanning or even be more sensitive [10,11].

According to some authors, the diagnostic accuracy of MRI is higher than CSF analysis for the specific biomarkers that distinguish AD from frontotemporal dementia (FTD) [12]. Other investigators have suggested that the combination of MRI with CSF analysis is the best option to diagnose early AD [8,13,14].

Electroencephalography is useful when it is necessary to differentiate AD from Creutzfeldt-Jakob disease or other prion diseases [8,15].

Lumbar puncture followed by CSF analyses can rule out normotensive hydrocephalus or neuroinfections [8].

In AD, tau-protein is elevated, including its phosphorylated fraction, while low amyloid- β levels are maintained. Assessment of the ratio between these proteins has sensitivity and specificity of at least 80 % [16]. Nevertheless, routine measurement of tau and amyloid in CSF is not currently recommended except for research purposes [8,16].

Genetic testing may also have some clinical value in the diagnosis of AD. However, identification of polymorphisms in amyloid protein precursor (APP) and presenilin genes remains an area of scientific research and it is promising mainly for patients with a positive family history [17,18].

In conditions of limited material resources, the application of the above approaches in the diagnosis of AD remains a challenge. This significantly affects the accuracy of the available arrays of epidemiological data and does not allow an adequate assessment of the needs for medical service in terms of human and other resources [4,8].

When analyzing global trends in prevalence and mortality from AD and other dementias, several regions can be identified where these rates are particularly high. These are Turkey, Brazil, countries from the Middle East and North Africa, as well as Southeast Asia.

The rate of dementia deaths increased by 148 % (140–157 %) between 1990 and 2016 in the world. Globally, in 2016, dementia was the fifth leading cause of death (2.4 million (95 % CI 2.1–2.8) deaths) after coronary heart disease, chronic obstructive pulmonary disease, hemorrhagic and ischemic stroke. In 2016, dementia deaths accounted for at least 4.4 % (95 % CI 3.8–5.1) of total deaths, with 8.6 % (95 % CI 7.4–10.1) of deaths occurring among septagenarians (2.2 million (95 % CI 1.9–2.6) deaths). According to the latest WHO data, AD

and dementia deaths have reached 14,196 cases or 2.5 % of total deaths in Ukraine [5].

Globally, dementia was responsible for 28.8 million (24.5–34.0) disability-adjusted life-years (DALYs). So, over the past 25 years, dementia was estimated to have increased from the 41st place in 1990 to the 23rd in the rating of the reasons for DALYs worldwide [5].

Dementia accounted for 1.2 % (95 % CI 1.0–1.4) of DALYs for all ages. At the age of 70, this figure was increased to 6.3 % (CI 5.4–7.5) DALYs (23.9 million DALYs, 20.1–28.6). More women than men died with dementia in 2016 (1.5 million, 95 % CI 1.3–1.8 versus 0.8 million, CI 0.7–1.0). Age-standardized mortality rates for females were also higher than for males, corresponding to a higher prevalence of females than males, suggesting female predominance not only because of a longer life expectancy among women.

The age-standardized global prevalence in women was 1.17 times (CI 1.17–1.18) higher than that in men in 2016, with much more women affected by dementia (27.0 million, 95 % CI 23.3–31.4) than men (16.8 million, CI 14.4–19.6) worldwide.

Aim

The aim of the work was to study the descriptive epidemiology of AD in the Odesa region.

Materials and methods

The study was carried out on the basis of the Regional Mental Health Center (Odesa) in 2016–2021.

The review of current literature was done with the use of PubMed, ORCID and EMBASE databases over a 5-year period through information search using keywords: “Alzheimer’s disease”, “epidemiology”, “Ukraine”, “Odesa region”.

Additionally, the data of the primary referral of patients with a verified diagnosis of AD were analyzed considering sex. A total sample size was 628 cases.

All patients were examined according to current clinical protocols using the MMSE scales. Additional analysis was carried out on subscales „Serial Subtraction” (7s subtraction, 5 scores maximum), “Language” (naming objects – Pen/Watch (2 scores), Repeating (1 score), 3-Stage Command (3 scores), Read and Obey (1 score), Write Sentence (1 score), Memory (Recall (3 scores), Orientation (answering questions about location in the space and time (maximum – 10 scores) and Visuospatial (Copy Design (1 score)) [19].

All patients were recommended to undergo brain MRI.

Statistical processing of the obtained data was performed by frequency analysis methods using standard MS Excel packages (Microsoft Inc., USA, Microsoft® Excel® 2021 MSO (version 2212.16.0.15928.20196) [20].

The population of the Odesa region was determined according to the State Statistics Service [21]. The population in the region as of January 1, 2021 was 2,368,107 people, including the urban population of 1,591,976 people, or 67.2 %, the rural population – 776,131 people, or 32.8 %. The population in the region was 2,389,200 people as of February 1, 2016.

Informed consent was not required due to retrospective character of the study.

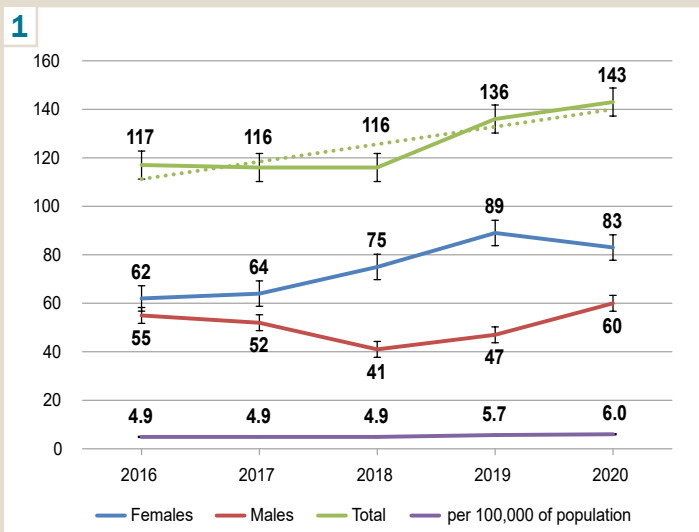


Fig. 1. AD incidence during the follow-up period (2016-2020).

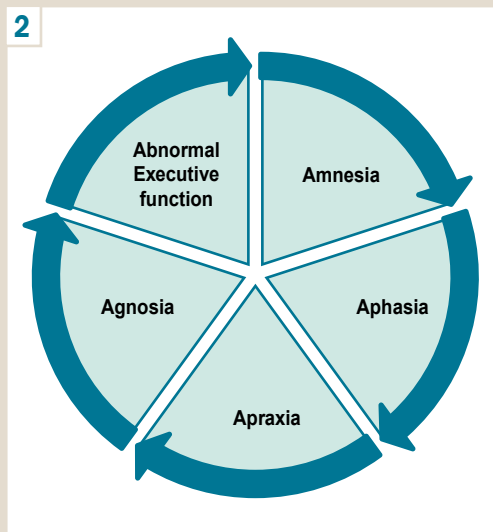


Fig. 2. Five A's of Alzheimer's [22].

Results

According to the retrospective analysis over the past 5 years, there was a constant increase in the number of identified patients with AD, from 4.9 cases per 100,000 population in 2016 to 6.0 cases in 2020 (Fig. 1). At the same time, a sex ratio throughout the analyzed period was stable, with a slight predominance of women (59.4 %) in the structure of cases. There were only 21 (3.3 %) octogenarians in the analyzed sample.

In all cases, the diagnosis of AD was established at the stage of manifested dementia. Meanwhile, it was an open question whether all cases verified as AD really corresponded to this diagnosis. However, given that an error in using outdated criteria from 1984 remained at the same level over the analyzed period, this possibility could be neglected.

Examinations of patients at the prehospital stage were often conducted fragmentary. Brain MRI was performed in 29 (4.6 %) patients, EEG in 41 (6.5 %) patients. A significantly larger number of patients (117 or 18.6 %) underwent brain computed tomography (CT), which, however, was inferior to MRI in terms of diagnostic accuracy. CT scans were faster and less expensive, helpful for patients who had difficulty lying flat or staying still and could be used in those with pacemakers. However, MRI was the preferred imaging method for early diagnosis because of its greater sensitivity and ability to differentiate dementia subtypes, especially for those with vascular lesions [9,10,22].

Actually, the diagnosis of AD was made on the basis of the clinical picture (deterioration of memory and other cognitive functions, behavioral changes). A neuropsychological examination using cognitive function assessment scales was performed for all patients included in the retrospective analysis.

The data of medical records allowed us to identify several main variants of the AD course. The classic variant (pentad: agnosia, anomia, aphasia, apraxia, amnesia) was observed in 369 (58.8 %) patients. In 114 (18.2 %) patients, pronounced manifestations of bradykinesia were noted amidst serious cognitive deficits. Another 45 (7.2 %)

patients, along with the classic manifestations of AD, had a pronounced tremor, both postural (37 cases or 5.9 %) and rest (8 cases or 1.3 %). It is believed that parkinsonian symptoms in patients with suspected AD indicate an alternative diagnosis. However, in all these patients, AD was confirmed by a medical council.

The commonest clinical presentation of dementia due to AD was memory impairment or more general disorganization of intellect. Memory problems usually were first noted by relatives than the patients themselves. Examples include missed appointments, unawareness of recent events, tendency to mix up times or to lose or misplace things. Mostly, cognitive decline manifested as loss of overall efficiency, failure to speak coherently or grasp essentials. Sometimes, relatives noticed subtle changes in personality as deterioration in manners or diminished awareness of the needs and feelings of others. Typical early signs were loss of interest and initiative, or inability to perform up to the usual standard, or minor episodes of muddle and confusion. Occasionally, the earliest change was noted as the exaggeration of long-standing personality traits such as suspiciousness or egocentricity.

A typical presentation of AD consisted of an early significant and progressive episodic memory deficit that remained dominant in the later stages of the disease and was followed by or associated with other cognitive impairments. They could be considered as the five A's of Alzheimer's: Amnesia, Aphasia, Apraxia, Agnosia and Abnormal executive function (Fig. 2).

Whatever the form of presentation, dementia could occur abruptly even though its evolution was insidious. Relatives could adjust to a slow decline until some sort of crisis forced them to realize the truth. As the disorder progressed, changes in emotional control and social awareness were also noted. Capacities for decision making, concentration and comprehension could also be impaired. Thinking became slow with mental fatigue. The content of thought turned out to be impoverished along with an inability to produce new ideas, and a tendency to follow set topics and memories from the past. Abilities to argue and reason

logically were impaired. Likewise, abilities to keep in mind various aspects of a situation simultaneously were also affected. Intellectual flexibility was lost leading to difficulty in shifting from one frame of reference to another. Abstract ideas presented especial difficulties and concepts tended to be interpreted in the most literal way. Judgement was impaired and patients could not be aware of their illness at all.

The average score on the MMSE scale was 18.6 ± 0.5 . The analysis on subscales showed the prevalence of memory, spatial orientation and verbal disorders. A significant number of patients (297 or 47.1 %) demonstrated slow progression after the onset of dementia.

Determined rates of AD prevalence indicated the underdiagnosis of this disease in the region. It should be noted that according to the HFA and GBD data, the prevalence of AD in neighboring countries was much higher [5]. Thus, in Romania, 2.56 % of the population suffered from dementia (whereas at least 60.00 % were represented by AD), in Turkey – 1.80 %. In Moldova, the number of patients with AD was estimated at 20,777 cases in 2021, with a significant increase in the number of cases in recent years [5]. We could assume that the levels of prevalence and incidence in the Odessa region would be comparable with these data, but we saw significant differences in practice.

Assessing the national population, we can note a small number of patients in the older age group (3.3 %) and a predominance of women (59.4 %). This fact can be explained by the rather low life expectancy of Ukrainians and the view that women live longer than men on average of 15 years.

Discussion

Assessment of the AD prevalence in Ukraine is quite difficult. Often, people around take this disease as normal age-related changes and patients never consult physicians. Unfortunately, the final diagnosis in such condition is frequently made only posthumously on the basis of a histopathological analysis of brain tissue.

The rate of AD-related deaths in the adult Ukrainian population is 0.3–0.5 per 100,000 people. Obviously, these rates are significantly underestimated. Thus, in the UK, AD caused 112 deaths per 100,000 people, in the USA – 82, in France – 76, and in Germany – 51 [4,5]. In countries bordering the Odessa region (Romania and Moldova), the mortality rate from AD was estimated at 40–60 cases per 100,000 population [5].

According to the National Statistics, the percentage of deaths from the nervous system dysfunctions in Ukraine is decreasing [20] but the mortality from AD shows an upward trend. Most likely, there is a possibility of an inaccurate calculation methodology here, since quite a few causes of death, such as AD, are included in official statistics. Ukraine ranks the 136th place (between Botswana and Cameroon) in the global rating of AD-related deaths.

On the one hand, our study has shown that the prevalence of AD in the Odessa region exceeded 4.5 cases per 100,000 population. On the other hand, this level has indicated underdiagnosis. Theoretically, any physician facing a patient with cognitive impairment should conduct a clinical neurological examination, supplemented by a neuropsychological study, blood tests for specific neurodestruction marker proteins, neuroimaging and other clinical

and instrumental examinations, which, according to national experts, are available in Ukraine. In practice, a significant part of patients diagnosed with AD does not undergo a full examination, and the diagnosis is made largely empirically.

The unavailability of high-resolution neuroimaging and CSF examination for highly specific proteins (tau and beta-amyloid) did not allow us to assert that all cases registered as AD really corresponded to this diagnosis [9–11]. However, even the available data were sufficient to talk about the need to change the principles of registration and epidemiological analysis of the entire spectrum of diseases accompanied by moderate cognitive impairment and dementia.

The presence of memory impairments and other cognitive process disorders, such as language, visuospatial perception, and personality is central to dementing the diagnosis in elderly patients. The task of detecting symptoms is simplified to some extent in the advanced stages of dementia; the diagnosis of dementia is much more challenging for clinicians when the symptoms are far less obvious. Equally challenging is the clinical distinction between different subtypes of dementia that present in similar manners, such as frontotemporal dementia for which no drug treatment is currently available. Because of its slow and insidious onset, the early stages of AD can be confused with relatively mild memory impairments that are associated with normal ageing. The early symptomatic phase of AD, commonly referred to as a mild cognitive impairment (MCI), can be indistinguishable on bedside clinical examination from normal ageing, but the disease is more readily identified by means of neuropsychological testing with or without an aid of other diagnostic procedures, such as CT, MRI or PET scans [23,24].

A pattern of regional brain atrophy helps to distinguish common neurodegenerative causes of dementia. Disproportional hippocampal atrophy suggests AD rather than vascular dementia or dementia with Lewy bodies, but there is overlap. Brain atrophy rates on serial MRI are increased (3–4 times) in AD as compared to normal ageing. A repeat scan after a year might clarify the diagnosis, especially MCI to AD conversion. Medial temporal lobe atrophy on MRI also differentiates AD from healthy ageing [9].

PET has recently been incorporated into dementia workup, and imaging agents that specifically bind the peptide amyloid-beta or the protein tau have been studied to determine their clinical applicability. The main risk of PET imaging is exposure to radioactive imaging agents, such as flurodeoxyglucose used as a radiotracer (FDG-PET) with a half-life of about 110 min. It permits in-vivo assessment of brain metabolism and supports detection of frontotemporal dementia, particularly when clinical evaluation is uncertain and there is little change on structural imaging. It shows focal frontal or temporal hypometabolism, or both [24,25].

Functional imaging is clinically helpful in distinguishing dementia with Lewy bodies from other causes of dementia because dopamine depletion can be detected by dopamine transporter (DAT) scans. In moderate dementia, when dementia with Lewy bodies is suspected, a normal DAT scan reliably excludes dementia with Lewy bodies [9,23,24].

As can be seen, a clinician needs both clinical skills and basic understanding of the neuroscience for an effective

dementia assessment. Cognitive testing is useful not only to assist in diagnosing dementia, but also as an objective baseline for tracking changes over a period of time. Finally, cognitive test is also helpful in monitoring treatment response [1,2,5,25–30].

Conclusions

1. The prevalence of AD in the population of the Odesa region was 6.0 cases per 100,000 population at the end of 2021, which was an order of magnitude less than the global average.

2. The average score on the MMSE scale was 18.6 ± 0.5 . The analysis on subscales has shown the prevalence of memory, spatial orientation and verbal disorders.

3. The Ukrainian population is characterized by the small number of patients of the older age group (3.3 %) and the predominance of female patients (59.4 %).

Prospects for further research are related to the creation of a regional register of neurodegenerative diseases based on interdisciplinary integration.

Conflicts of interest: authors have no conflict of interest to declare.
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