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Clinical Features of Subjective Cognitive Decline in The Early Stages of Alzheimer's Disease

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Abstract: Subclinical stage of the disease precedes the clinical stage of moderate cognitive decline in Alzheimer's disease (AD). Subjective cognitive decline (SCD) — a condition in which the level of cognitive function habitual for the subject gradually begins to decrease. In 2021, researchers from the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for the diagnosis of SCD have been proposed, as well as features that increase the probability of preclinical stage AD in patients with moderate cognitive impairment have been identified. Patients should be offered a complex of examinations — questionnaires regarding the impact of memory impairment on current cognitive activity (forgetfulness, searching for things, difficulty finding words, etc.), testable self-report of cognitive dynamics, neuropsychological testing and diagnosis of pathopsychological changes such as depression and anxiety. It would appear that counselling in the form of interviews and/or testing of persons able to provide relevant information about the patient should be included in the examination of patients with complaints of memory disorders, regardless of their degree of severity. It may be necessary to conduct a survey on the patient's daily activity, ability to self-service (score, orientation, planning, control and so on), as well as to obtain information about any memory-related changes that have become visible to others, because it is the data from the partner/relative that increase the predictive value of the diagnostic. The modern approach to the study of cognitive functions in elderly people without dementia in the long-term is certainly able to help identify people with a high risk of developing AD.

Keywords: *Alzheimer's disease; cognitive impairment; subjective cognitive decline; dementia.*

Introduction

Alzheimer's disease (AD) is the most common cause of cognitive deficiency in persons over 65 years of age, causing almost 80% of cases of dementia [1; 2]. Neuroscientists and psychiatrists around the world face the challenge of clarifying clinical and pre-clinical manifestations of this disease. In 1907, Aloysius Alzheimer described for the first time in detail the clinical case of a 51-year-old patient Auguste Deter, who was under his supervision at the Frankfurt am Main City Hospital, performing a histological examination of her brain by silver staining [3]. The result of this study was the discovery of neural plaques, neurofibrillary tangles and amyloid angiopathy, which later became the hallmarks of neurodegenerative disease, which is now named after its discoverer [4]. This allowed the medical community throughout Europe and the United States to diagnose this pathology by 1911 [5]. The screening revealed a high correlation of the AD with the results of standard cognitive deficit tests [6;7]. A significant breakthrough in the diagnosis and assessment of clinical manifestations of all types of dementia has been the realization that cognitive impairment varies depending on the etiology of the pathological process. The beginning of etiologically differentiated treatment of dementia is connected with the name Martin

Albert, who, together with the employees, in 1974 dedicated «subcortical» and «cortical» types of dementia. It has been shown that in «subcortical» dementia, typical of patients with progressive supranuclear palsy, cognitive impairment, consisting in forgetfulness, slow thought processes, personality changes with apathy or depression, was detected, as well as impairing the ability to use the knowledge gained. Similar clinical manifestations have also been described in patients with Huntington's disease. This clinical presentation differed significantly from that of cortical dementia, also typical of AD [8]. Subsequent studies have only confirmed qualitative differences between «subcortical» and «cortical» forms of dementia. The result was the separation of these forms of dementia as two clinical syndromes. The role of various pathological proteins in AD development has been the subject of debate among researchers. According to the «amyloid theory», beta-amyloid (Aβ) causes neuronal stress with subsequent degeneration of neurons and the formation of paired spiral filaments consisting of a hyperphosphorylated tau protein (P-tau). In this case, the process of hyperphosphorylation of tau is the consequence of the «cortical load» Aβ, reaching a critical threshold [9]. According to the «tau-protein» theory, the basis of the neurodegeneration process is lies the breakdown of intracellular tau protein, secondary damage to neurons, the release of protein filaments into the extracellular space and their aggregation. Many researchers believe, this is a sign that P-tau is responsible for much of the degeneration in AD, although it does not rule out the role of Aβ (formation of amyloid «plaques») in exacerbating the neurotoxic effect [10]. B. Dubois et al. [11] combines markers indicating the presence of tau pathology or amyloid pathology into a group of AD pathophysiological markers as equivalents, and atrophic changes and metabolic changes according to positron emission tomography (PET) data - into a group of topographic markers as mandatory lifetime evidence of AD.

Researchers of the National Institute on Aging and Alzheimer's Association (NIA-AA) divide the markers of the disease into three groups: biomarkers of the Aβ deposit, biomarkers of neuronal damage, associated biochemical changes [12]. The main biomarkers of the spinal fluid (amyloid-β42 (Aβ42), common tau, and P-tau) are now considered to be confirmed predictors of AD progression [13]. Atrophy of the medial regions of the temporal lobes (in particular, atrophy of the hippocampus) is considered the most visible marker on magnetic resonance imaging (MRI) indicating a shift from mild cognitive impairment to AD [14]. In 2015, J. Toledo et al. [15] in a seven-year cohort study found that in patients with subjective cognitive complaints about memory during long-term follow-up, in 27.6% of cases, executive function disorders and cognitive changes in one or more areas developed (score, orientation, writing, reading) to the degree of moderate cognitive impairment (MCD). Some researchers have found a relationship between early Aβ deposition and the ability to perform traditional standardized cognitive tests, the amount of brain matter and the educational level (cognitive reserve in patients) and AD development [16 -19]. In 1976, Katzman [20] conducted a series of studies and identified the histopathological identity of senile and presenile dementia, and based on epidemiological data, concluded that AD is the fourth leading cause of death among elderly. AD was removed from the category of rare diseases. Therefore, its description and treatment are one of the most important public health problems.

Dementia development at the Alzheimer's disease

In research in the 1990s., amnesia was confirmed to be the early and significant sign of dementia syndrome in AD (consistent with pathology studies showing that the most involved in the pathological process the medial temporal lobe structures appear - hippocampus, entorhinal cortex) [21]. The memory deficit was manifested in the inability to efficiently process and store new information, the first suffering was the delayed memory [21]. According to Amiev et al. [22] in a 14-year case-control cohort study, the first measurable cognitive decline was semantic verbal fluency, which begins to decline 12 years

before the diagnosis of dementia in AD. Despite it, many gaps remain, especially in the clinical features of the pathology.

In 2011, NIA-AA proposed new criteria for clinical diagnosis of AD. Three stages of the disease have been identified: pre-clinical, mild cognitive impairment (MCI), dementia [23, 24].

The pre-clinical stage is of most interest to modern researchers due to the low level of knowledge, insufficient diagnostics, and the ability to initiate therapy at very early stages of the degenerative process, which allows the development of approaches, related to the prevention of dementia [25; 26].

According to NIA-AA, the basis for determining the pre-clinical stage of the AD is:

- identification of biomarkers in neuroimaging and laboratory studies: Aβ, tau protein, P-tau;
- evaluation of neurodegenerative changes;
- estimate of cognitive deficiency.

NIA-AA researchers suggested dividing the pre-clinical stage into several phases (Table 1) [27, 28].

Table 1. Staging categories for preclinical Alzheimer's disease research

Stage	Features	
Stage 1	Asymptomatic cerebral amyloidosis	High PET amiloid tracer retention Low CSF (cerebrospinal fluid) Aβ42
Stage 2	Asymptomatic amyloidosis + "downstream" neurodegeneration	Neuronal dysfunction on FDG (fluorodeoxyglucose)-PET/fMRI (functional magnetic resonance imaging) High CSF tau/p-tau Cortical thinning (posterior cingular, precuneus and / or temporoparietal cortex)/hippocampal atrophy on sMRI (structural magnetic resonance imaging)
Stage 3	Amyloidosis + neuronal injury + subtle cognitive/behavioral decline	Evidence of subtle change from baseline level of cognition Poor performance on more challenging cognitive tests Does not yet meet criteria for mild cognitive impairment

Formation of perceptions about subjective cognitive decline

The onset of the disease is related to the patient's subjective sense of cognitive impairment. The point at which a person passes from the asymptomatic stage to the symptomatic pre-dementia stage or from the symptomatic pre-dementia stage to the beginning of dementia stage is difficult to determine [29].

In 1982, Reisberg et al. [30] suggested that the clinical stage of mild cognitive decline in AD is preceded by the subclinical stage of the disease: subjective cognitive decline (SCD). This is a state in which the level of cognitive function habitual for the subject gradually begins to decrease. Various terms were used to characterize SCD: subjective cognitive complaints, subjective complaints about memory, subjective memory problems, subjective memory impairment, subjective cognitive impairment, loss of subjective memory, impaired subjective memory [31].

In order to better understand the state of the SCD as a pre-clinical stage, its symptoms should be distinguished from various subjective complaints about memory. The latter are

commonly referred to as subjective cognitive complaints (SCCs) which are related to personal experience of cognitive impairment and which is currently the criterion for diagnosing mild cognitive decline [32, 33, 34]. It is recommended that the criterion for separating MCI and SCS be a decrease in neuropsychological test scores by more than 1.5 sigma compared to normal age, gender, and educational characteristics [35]. However, there is uncertainty as to which patient complaints are most relevant for identifying very early cognitive decline [33]. Some Russian authors identify a state of lightweight cognitive decline (LCD), characterized by a small (less than 1–1.5 sigma) decrease in some indicators with extended neuropsychological treatment [35-38].

In 2014, Jessen et al. proposed clinical criteria for diagnosing subjective cognitive impairments, as well as identifying features that increase the likelihood of pre-clinical stage AD in patients with mild cognitive impairment (Table 2) [33;39].

Table 2. Criteria for diagnosis of subjective cognitive decline

Confirming	Excluding
The constant decline in cognitive functions experienced in-house compared to the previously normal state and not associated with an acute brain disease. Against this background are normal results based on age, gender and education in standardized cognitive tests, which are used to confirm moderate cognitive impairment or prodromic AD.	Mild cognitive impairment, prodromic stage of AD or dementia, mental disorder or neurological disease (other than AD), taking drugs that can reduce cognitive ability or use of psychoactive substances.
Features that increase the likelihood of pre-clinical AD in patients with subjective cognitive decline (SCD+) [39]	
Subjective memory loss regardless of other cognitive functions.	
Subjective cognitive decline identified within the last five years.	
The SCD is 60 years old.	
Concerns (concerns) related to the SCD.	
Confirmation of cognitive decline by the observer (relative, neuropsychologist).	

The diagnosis of SCD is based on self-esteem, which can easily be influenced by emotional factors such as anxiety, depressive and prematurity of personality [30]. Complaints of memory loss in themselves cause physical and mental suffering to the patient, which undoubtedly increases the level of stress.

Epidemiology of the subjective cognitive decline

It has long been postulated that SCD begins to form 15 years before mild cognitive impairment - MCI [30]. In some long cohort observational studies of patients with developed clinical dementia, it has been established that one hundred SCD occurs (on average) 10 years before AD [40 - 43].

Individual long-term cohort studies have shown that patients with more pronounced memory complaints show a more drastic decline in episodic memory testing over time [44; 45] and a decrease in the total according to cognitive screening tests [46, 47].

The first cohort studies determined the prevalence of SCD from 12.3% [48] to 84.5% [49]. According to a meta-analysis of 28 studies conducted by A. Mitchell and co-authors

[50] elderly with memory loss complaints were found to be twice as likely to develop dementia as those without subjective complaints.

Cohort observations of healthy elderly during 7 years showed that SCD is associated with a 4.5-fold increase in the risk of MCI development and a 6.5-fold increase in the risk of possible AD development [51-53].

According to other researchers, approximately 2.3% to 6.6% [50] or even 11% [54, 55] among elderly patients with subjective cognitive complaints, over time, show progression of the disease to MCD and dementia. In this case, the conversion of SCD to MCI for 5 years is 34.2% [50].

At the same time, Roehr et al. [56] and Hao et al. [57] could not find any connection between cognitive impairment and dementia.

Screening methods of memory research, neuropsychological diagnostics, pathopsychological diagnostics of subjective cognitive decline

Many authors prefer psychometric approach to diagnostics of cognitive decline. It is objective, less subject to fluctuations related to clinical representation and somatic condition of the patient, and contributes to the standardization of diagnostic criteria [58, 59]. It is noted that clinicians should be alert to "small" signs of cognitive decline, such as weakened interest in the environment, absent-mindedness, rapid fatigue, decreased memory for current events, inability to remember new names, problems with orientation in unfamiliar areas, difficulties in choosing a word when speaking, difficulties in counting operations, passivity, desire to shift responsibility to the spouse, daytime sleepiness, irritability [60, 61].

The experience of the authors of this work [62] suggests that the use of screening techniques (Mini-mental state examination (MMSE), Montreal Cognitive Assessment (MOCa), clock drawing test and so on) is quite feasible and even necessary, but not enough. It should be borne in mind, however, that the screening tests for the minimum cognitive impairment are insensitive [45; 63; 64] and patients are then able to perform these tests above the threshold required to cognitive decline [39]. In a clinical setting, the difference between SCD and MCI can only be identified by using advanced psychometric tests [29; 33].

It is important to understand that subjective cognitive changes are detected over a long period of time, and neuropsychological tests measure individual performance at a given point in time. Thus, for some older persons with SCD, average neuropsychological test scores will actually reflect stable functioning (no decrease), while for others average scores will reflect a slight decrease, compared to a higher baseline [65]. In a study by Koppara et al. [66; 67] the «Memory Clinics» patients with subjective cognitive complaints showed a slight loss of memory when performing the «Short-term-binding task» compared to the control group [68].

B. Dubois with co-authors [69] believe that SCS can be detected using the «Episodic memory test» or «Cognitive composite scale», which are recommended as a marker for clinical debut of Alzheimer's disease. Smart & Krawitz [70] have researched the Iowa Gambling Task (IGT) to this end. Patients with SCD in the series of tests, demonstrating generally similar results to the control group in repeated testing did not take the experience into account in decision making. It may suggest that patients have functional impairments with «updating/working memory» (updating/working memory), or they quickly forget the experience gained from trying to test. IGT is used as a convenient model for studying forecasting processes [71].

In 2012, Rabin et al. [72] considered a combination of three cognitive assessment methods - neuropsychological characteristics, self-reporting, and intimate interviews. The results showed that «Free and Cued Selective Reminding Task with Immediate Recall» (FCSRT- IR) and «Logical memory delayed recall», «Digit symbol substitution test» [73;

74], as well as self-questioning and interviewing of relatives about cognitive problems contributed to predicting AD in in older people with MCI.

However, the authors found that some parameters (psychomotor response rate, self-esteem) are unstable and cannot serve as a «diagnostic signal» to the presence of SCD. The FCSRT-IR is thought to be suitable for differential diagnosis of age-related physiological changes and for neurodegenerative changes in AD. Cognitive reports based on family surveys may be better predictors of objective outcomes than self-report, and may assist in detecting very early neurodegenerative decline, in addition to the most predictable neuropsychological variables [68; 69; 75].

In a three-year study by Jessen et al. [76] found that cognitive impairment and clinical anxiety were positively correlated with risk of dementia. Increasing stress is correlate with increased cortisol levels, which in turn correlates with increased risk of cognitive decline and AD development. This is confirmed by the fact that subjects with dementia and MCI at BA have been found to have higher levels of cortisol in cerebrospinal fluid than in healthy people. Cortisol is known to have neurotoxic effects on the hippocampus and contribute to the growth of oxidative stress and toxicity of amyloid β-peptide [77; 78].

These results suggest that qualitative characteristics of subjective cognitive decline, persistently lasting for a long time, have a predictive value for AD dementia (apart from complaints as such). Screening estimates explain the variability of SCS symptoms and traits in real time by assessing the relationship between cognitive functions and other relevant variables (e.g., stress, pain, mood) which may be important for explaining variations in subjective cognition [72]. Significantly, some researchers argue that subjective cognitive decline reflects only the current affective status of a person or the general trend towards stress rather than foreshadowing future cognitive decline [79]. In 2015, Buckley et al. [80] reviewed the literature on SCD. The results revealed different clinical characteristics of normal seniors with complaints of reduced cognitive function compared to patients with MCI and dementia in AD. With regard to complaints, healthy older persons usually mentioned memory problems, including difficulties in finding words and names. In addition, clinically normal elderly often reported anger, frustration, or irritation due to perceived memory lapses, reflecting their continued insight and informed understanding of their cognitive problems [80]. Buckley and colleagues have also found that subjective cognitive decline correlates with greater depressive symptoms and smaller amounts of left hippocampus [81].

Development of questionnaires to identify subjective cognitive decline

Vogel with co-authors [82] developed neuropsychometric self-report screening. The test takers were asked to answer the following question: «You are concerned that you are experiencing a significant decline in your mental faculties, which worsen more than people your age? ».

Similar to the «The Memory Complaint Questionnaire» (MAC-Q) and the «The Subjective Memory Complaints Scale» (SMC) are used to test the SCD, in which self-report memory and attention when solving everyday tasks.

MAC-Q [83] is a short six-point scale where participants answer questions comparing their current memory performance with the time, they were young (in this study they were asked to compare themselves to the current 20-year-old). Each element has a rating on a 5-point Likert scale from «Now much better» to «Much worse now». Points (in the 7-35 range) are summed (total MAC-Q) with doubling points for the latter (Table 3). Higher self-esteem scores for memory-impaired individuals indicate a more subjective perception of their own decline.

Table 3. «The Memory Complaint Questionnaire» (MAC-Q)

- Remembering the name of a person just introduced to you.
- Recalling telephone numbers or zip codes that you use on a daily or weekly basis.
- Recalling where you put objects (such as keys) in your home or office.
- Remembering specific facts from a newspaper or magazine article you have just finished reading.
- Remembering the item(s) you intend to buy when you arrive at the grocery store or pharmacy.
- In general, how would you describe your memory compared to when you were in high school?

The SMC includes 10 questions related to violations of daily memory with a total score of 0 (no complaints) to 21 (Table 4).

Table 4. The Subjective Memory Complaints Scale

No.	Questions regarding memory impairment affecting daily activities	Score
1.	Do you have any complaints about your memory?	0–3
2.	Do other people think you're forgetful?	0–2
3.	Do you ever forget the names of family members or friends?	0–3
4.	How often do you forget where things are?	0–3
5.	Do you often use notes to remember things?	0-2
6.	Have you ever had difficulty finding specific words?	0-1
7.	Have you ever been disoriented in your neighborhood?	0-1
8.	Are you thinking slower than before?	0-2
9.	Do your thoughts ever get mixed up?	0-2
10.	Do you have any trouble concentrating?	0-2

An attempt was made to define a methodological approach for diagnosing the SCD. It has been found that different scales of measurement of subjective complaints are not interchangeable when used in cohorts of patients with memory and attention disorder. In general, a wide range of evaluations of both the «The Subjective Memory Complaints Scale» and «The Memory Complaint Questionnaire» and the results of both scales were not related to the degree of cognitive impairment in testing. It follows that in a cohort of patients with mixed genesis memory disorder, the intensity of cognitive complaints cannot be assessed in isolation for diagnosis, that is, they cannot be considered outside the aggregate data on memory characteristics of patients obtained from other sources.

Jessen et al. [65] attempted to incorporate qualitative features into the SCD categorization system. In the German study «Aging, cognitive functions and dementia» participants were asked: «Do you feel that your memory is getting worse?». The following answers were offered: no; yes, but I am not concerned; yes, I am concerned. Those who reported «memory loss with anxiety» were rated as having a subjective cognitive disorder. Koppara et al [67] showed that patients who reported concerns about their memory on

questionnaires showed greater declines in episodic memory on neuropsychological testing, but there was no significant decline in verbal fluency or working memory. Rabin et al. [72] believed that studies of cognitive functions should be carried out repeatedly and compare the results over time. However, it is indicated that for older adults (≥70 years), SCS is a normal part of aging and not a memory problem [57].

Conclusions

Thus, there is currently no consensus on how to assess or classify the SCD [84]. It can be concluded that, in addition to visualization methods of diagnosis, patients need to offer a set of additional tests - clinical diagnosis, tested self-report cognitive dynamics, neuropsychological testing and diagnosis of pathopsychological changes. It appears that the examination of patients with complaints of memory disorders, regardless of their severity, should include consultation in the form of interviews and/or testing of persons capable of providing relevant information about the patient. It may be necessary to conduct a survey on the patient's daily activity, ability to self-service (score, orientation, planning, control, etc.), as well as to obtain information about any memory-related changes that have become visible to others, because it is the data from the spouse/relative that increase the predictive value of the study. A modern approach to the study of cognitive functions in older people without dementia in the long term can certainly help identify people with high risk of developing MCI and AD.

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