Subjective and functional cognitive impairment: diagnostics using biological markers of Alzheimer's disease

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Cognitive impairment (CI) is one of the most common disorders in elderly. The development of dementia is usually preceded by subjective (SCI) and mild cognitive impairment (MCI) over several years. Patients with SCI are at increased risk of developing MCI and dementia, but SCI may not progress for a long time and in many cases is functional in nature (functional CI – FCI). The article discusses the manifestations and diagnostic issues of SCI and FCI and the possibilities of diagnosing Alzheimer's disease (AD) at the SCI stage using biological markers for AD in cerebrospinal fluid (CSF). The article presents the results of a long-term follow-up (more than 4 years) of two patients with SCI who showed no significant disturbances in repeated neuropsychological examinations. In one patient with SCI, positive biological markers for AD were found in the CSF, indicating an early (second) stage of AD, while in the other patient the absence of these markers indicated a functional nature of the CI. The article discusses the treatment of patients with SCI and the possibilities of anti-amyloid therapy when the Alzheimer's nature of CI is detected.

Keywords: *cognitive impairment; subjective cognitive impairment; functional cognitive impairment; Alzheimer's disease; biological markers of Alzheimer's disease.*
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Cognitive impairment (CI) is one of the most common disorders in the elderly. Severe CI (dementia) is observed in 5% of the elderly population. According to forecasts, in 2050 the number of patients with dementia may exceed 150 million [1]. There are a lot of diseases that can lead to the development of dementia, but the majority (70–80%) of cases of dementia are Alzheimer's disease (AD), cerebrovascular diseases and their combinations [2].

The development of dementia is usually preceded by subjective (SCI) and mild cognitive impairment (MCI) over several years [2]. MCIs are cognitive impairments identified by neuropsychological examination that do not result in the loss of functional activity but may cause difficulties in learning new forms of daily activities [3, 4]. The prevalence of MCI increases with age, accounting for 6.7% at the age of 60–64 years and 25.2% at the age of 80–84 years [3].

Diagnosis of the CI etiology, use of biological markers for AD

Diagnosis of the presence and degree of CI is based on a detailed assessment of the history of the disease and complaints from both the patient and those around him (relatives, friends), anamnesis data, results of neuropsychological examination, assessment of the impact of cognitive impairment on everyday functional (professional, social, domestic) activity [2]. In the case of dementia, there are significant difficulties in at least one area of everyday life, while with MCI, patients may experience minimal difficulties compared to their past experience, which do not limit their independence.

In case of detection of CI, in order to identify its possible causes and exclude concomitant conditions/diseases that aggravate CI, it is necessary to conduct a laboratory examination, including general blood and urine tests, examination of biochemical blood parameters, lipid profile, determination of the level of thyroid hormones, vitamin B_{12}, folic acid in the blood serum. It is necessary to assess the emotional state of patients with CI (anxiety, depression, other neuropsychiatric disorders).

Neuroimaging studies: computed tomography (CT) or magnetic resonance imaging (MRI) of the brain can identify the cause of CI in some diseases (cerebrovascular diseases, tumors, subdural hematoma, normal-pressure hydrocephalus, etc.). AD is characterized by atrophic changes, which are most often observed in the medial parts of the temporal lobes and parietal regions of the brain. However, it should be noted that atrophic changes are often observed in healthy elderly and senile people.

In recent years, biological markers have been used to diagnose AD; based on these data, several stages of AD have been proposed (see the Table) [5]. AD is characterized by a decrease in the concentration of beta-amyloid (low $A\beta_{42}$ level, an increase in the $A\beta_{40}/A\beta_{42}$ ratio) and an increase in the levels of

total and phosphorylated tau protein in the cerebrospinal fluid (CSF), pathological accumulation of beta-amyloid and tau protein in the brain according to positron emission tomography [5, 6]. The simplest and relatively inexpensive method is CSF analysis, which is beginning to be used in our country and allows us to establish or exclude AD in many diagnostically complex cases [7–10].

Subjective cognitive impairment

Currently, the number of people concerned about the loss of memory and/or other cognitive functions (CF) is increasing, which is a reason for visiting a doctor [11]. In 20–30% of patients who visit specialized clinics (memory clinics) with complaints of cognitive decline, neuropsychological examination does not reveal any deviations from normal test results [12], which is regarded as SCI. The prevalence of SCI increases significantly with age: among people aged 70 years and older who show normal results of neuropsychological testing, more than a half (50–80%) present with cognitive complaints [13].

In 2014, an international group of experts proposed an initiative to identify SCI [14]. According to the proposed criteria, patients with SCI are characterized by, firstly, a feeling of gradual (not acute) decline in cognitive abilities (primarily memory impairment); secondly, no changes in standardized neuropsychological tests (taking into account the age and level of education); and thirdly, normal daily activity [14]. This distinguishes them from patients with MCI and severe CI (dementia), in whom the presence of cognitive deficit is confirmed by the results of an objective examination, and in dementia case leads to a decrease in daily (professional, social, domestic) activity.

SCI are not distinguished in the latest International Classification of Diseases, 11th Revision (ICD-11), or in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Patients with SCI are considered healthy people, whose complaints may reflect age-related deterioration of CF [15]. In a significant proportion of cases, regression of complaints is observed over time [15].

Among patients with SCI, whose complaints reflect age-related deterioration of CF and cause psychological distress and fear of developing dementia, the majority are people whose complaints are associated with increasing age [14, 15]. In many patients, SCI is caused by emotional disorders (anxiety, depression), stressful events, chronic pain syndromes, and complications from taking medications. However, a significant proportion are patients with developing neurodegenerative (AD, frontotemporal degeneration, dementia with Lewy bodies, etc.) or cerebrovascular diseases, as well as other organic pathologies of the brain. SCI can be caused by diabetes mellitus, arterial hypertension, vitamin B_{12} deficiency, and other somatic diseases. In cases where there are no neuropsychiatric or somatic reasons that can explain the cognitive deficit, and relatives or close people note a decrease in the patient's cognitive level, the likelihood of developing AD or another neurodegenerative disease increases significantly [15].

To determine the causes of SCI development, it is important to find out what kind of CI causes concern in the patient (impaired memory, speech, concentration, orientation, visual-spatial functions, executive functions), whether emotional (anxiety, depressive) or other neuropsychiatric disorders, concomitant diseases (for example, chronic pain syndromes, chronic insomnia, stressful situation) are noted, whether alcohol or psychotropic drugs are consumed. SCI can be misdiagnosed if only basic (usually brief) neuropsychological tests are used in a neuropsychological examination – the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA-test), the Clock Drawing Test (CDT). In the case of SCI, a complete neuropsychological examination is necessary to identify changes and establish the development of MCI syndrome [14, 15].

Epidemiological studies have shown that the presence of SCI is associated with the risk of progression of CI, development of MCI, and subsequently dementia [16]. The progression of SCI to MCI within a year averages 6.7%, progression of SCI to MCI or dementia occurs on average over 15 years [17]. In patients with SCI, the risk of developing MCI is increased by 4.5 times, the risk of developing AD is 6.5 times compared with people who do not complain of cognitive decline [18]. In those cases where biological markers of AD are detected in patients with SCI, the risk of progression of CI to MCI and dementia significantly increases [19].

It is proposed to identify a form of SCI+, which has a higher probability of progression and includes [15]: subjective memory loss with the preservation of other CFs, duration of complaints no more than 5 years, age 60 years and older, concern about the presence of disorders, persistence of disorders, seeking medical help, confirmation of forgetfulness from relatives or friends who have been observing the patient for a long time.

A study of biological markers of AD shows that changes characteristic of AD are found in 7–40% of patients with SCI, with their frequency being higher among patients with SCI+ [15]. Observation of patients with SCI and the presence of biological markers of AD show that approximately half of them develop MCI or dementia within 3 years [20]. According to some authors, the detection of biological markers of AD in patients with SCI allows us to regard this condition as an early clinical stage of AD, preceded by an asymptomatic stage of AD [5, 6, 15].

We present our own clinical observation.

Patient M., *67 years old, first came to the Clinic of Nervous Diseases of Sechenov University in September 2020 with complaints of memory loss and concentration problems over the past two years. The patient has a higher education, specializing in engineering and mathematics, and continues to work. He has been suffering from arterial hypertension for 10 years, regularly takes valsartan 80 mg/day, blood pressure (BP) is maintained at 130/80 mm Hg.*

Stages of AD when biological markers of the disease are present (according to [5], with changes)

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Asymptomatic	SCI	MCI	Mild dementia	Moderate dementia	Severe dementia

Height – 182 cm, body weight – 82 kg. Neuropsychological examination did not reveal significant deviations from the norm. According to the MMSE, the patient scored 28 out of 30 points, according to the Frontal Assessment Battery (FAB) – 16 out of 18 points. The CDT – 10 points. The 12-Word Test: with immediate reproduction, 8 words were independently named and 4 with a semantic categorical hint (a total of 12 words), with delayed reproduction, 7 words were independently named and 5 words with a hint (a total of 12 words). In the Word fluency test (literal association), the patient named 20 words starting with the letter "s", the number of words in the categorical association test was 12. The nominative function of speech (naming images of objects) is not impaired (two phonemic cues in Boston Naming Test (BNT). Trail Making Test (TMT), Part A – 68 sec, Part B – 110 sec. Mild depression (18 points on the Beck Depression Inventory), severe personal anxiety (49 points) and mild situational anxiety (38 points) on the Spielberger Anxiety Inventory were detected.

General and biochemical blood tests, general urine analysis did not reveal any clinically significant changes. Vitamin B_{12} and folic acid levels were normal. MRI of the brain revealed signs of cerebral microangiopathy (stage I according to the Fazekas scale), score 1 according to the Visual Rating of Medial Temporal Lobe Atrophy (MTA 1).

Thus, based on the examination results, SCI was diagnosed against the background of emotional-affective disorder (mild anxiety and depression).

During the observation of the patient for 4 years, no disturbances were noted during repeated neuropsychological examinations, all results of the tests remained normal. For example, after 4 years, the 12-Word Test: with immediate reproduction, he named 5 words and 7 with a hint (a total of 12 words), with delayed reproduction – 6 words and 6 with a hint (a total of 12 words). When assessing the emotional state, there are no signs of depression according to the Beck Depression Inventory (9 points), there is mild personal anxiety (42 points) and low situational anxiety (30 points) according to the Spielberger scale. Repeated MRI of the brain did not reveal any new changes. The patient continues to work, but has difficulties in renaming files on the computer, making tables, and is concerned about progressive forgetfulness.

The CSF was examined using electrochemiluminescence analysis (Roche Diagnostics on the Cobas e 601 analyzer in accordance with the approved methodology), which revealed a decrease in the level of beta-amyloid ($A\beta_{42}$ – 742.9 pg/ml with the norm >1030 pg/ml), normal levels of total (146.9 pg/ml with the norm <300 pg/ml) and phosphorylated tau protein (12.9 pg/ml with the norm <27 pg/ml).

Thus, the patient had no changes in CF during repeated neuropsychological studies and no progression of brain damage according to MRI data for a long time, but the patient himself noted the progression of CI, and biomarkers of AD were detected during the study of CSF, therefore the condition was assessed as SCI against the background of Alzheimer's pathology (second stage of AD).

Functional cognitive impairment

FCI is established in cases where, after a long-term observation of the patient, it is not possible to identify a disease that explains his complaints [21, 22]. According to the neuropsychological examination, in most cases, SCI or MCI are initially determined, or, much less frequently, dementia (see the figure), however, subsequent long-term observation demonstrates the absence of CI progression and the patient's accentuation of his complaints, which suggests FCI [23]. Fluctuations in the severity of CI, the absence of diseases causing CI and biomarkers of neurodegenerative disease confirm the functional nature of CI [23]. Patients with FCI are characterized by complaints of decreased memory and concentration, periodic "memory lapses" [22, 24].

The frequency of FCI ranges from 12% to 56% of all cases of primary visits to specialized memory clinics [23]. FCI may remain stable, progress (in rare cases – to the degree of dementia) or completely regress; in most patients, FCI may be associated with provoking factors (chronic pain syndromes, stress conditions, emotional disorders), but in some cases it is not possible to find the causes explaining changes in CF [23].

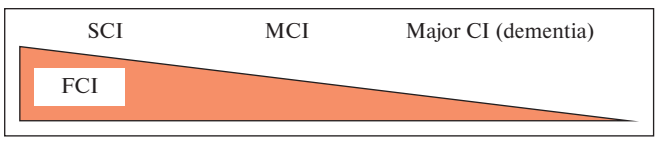
The diagnosis of FCI is very problematic, especially at an early stage, when a patient first consults a doctor. It is necessary to take into account the possibility of functional symptoms at the onset of various neurodegenerative, somatic and psychiatric diseases. A persistent course or even progression of CI, which is possible with FCI, requires the exclusion of other causes of cognitive decline. Therefore, most doctors in such cases prefer the diagnoses of SCI or MCI, taking into account the possibility of a misdiagnosis of FCI. In memory clinics, FCI is determined only in cases of long-term (at least 6 months) observation of the patient, if no other cause of CI is detected [23]. Patients with FCI are distinguished from patients with SCI by the presence of pronounced complaints of cognitive decline, the belief in the presence of serious problems, despite the doctor's explanations about the absence of a brain disease [23].

The presence of depression, anxiety or somatoform disorders is often accompanied by cognitive complaints and CI during testing, but experts suggest that they be regarded as pseudocognitive and not classified as true FCI [23]. In specialized memory clinics, emotional (depressive, anxiety) disorders are found in almost half of patients with suspected FCI; in such cases, CI is not usually regarded as functional [21].

It is important to note that DSM-5 identifies functional neurological disorders (sensory and motor). Currently, the following criteria for FCI as a subtype of functional neurological disorders have been proposed: 1) the presence of CI in one or more areas; 2) internal inconsistency (the appearance of disorders only in certain situations); 3) the absence of somatic, neurological or psychiatric diseases explaining CI; 4) clinically significant patient's distress and/or impairment in professional, social or other important areas of functioning, a feeling that further medical examination is necessary [23].

We present our own clinical observation.

***Patient Zh.**, 63 years old, has been complaining of decreased memory for current events and decreased concentration for 8 years. The patient forgets where she puts things, notes difficulties in finding words in conversation, but there are no disturbances in social and everyday activity. She first came to the Clinic of Nervous Diseases of Sechenov University in April 2021. The patient has a higher education, specializing in engineering. She is currently retired.*



FCI in the structure of cognitive disorders

On examination at our clinic: height – 165 cm, body weight – 68 kg. Blood pressure – 120/80 mm Hg. Neuropsychological examination did not reveal significant deviations from the norm. According to the MMSE, the patient scored 28 out of 30 points, according to the FAB – 16 out of 18 points. The 12-Word Test: with immediate reproduction, 10 words were named, with a semantic categorical hint – 2 words (a total of 12 words), with delayed reproduction, 8 words were named, with a hint – 3 words (a total of 11 words). Praxis and gnosis are not impaired. The CDT – 9 out of 10 points. In the Word fluency test (literal association), she names 15 words starting with the letter "s", the number of words in the categorical association test was 15. The nominative function of speech (naming images of objects) is not impaired. Trail Making Test (TMT), Part A – 60 sec, Part B – 80 sec. When assessing the emotional state, there are no signs of depression according to the Beck Depression Inventory (10 points), there is subclinical depression according to the Hospital Anxiety and Depression Scale (HADS), severe personal anxiety (49 points) and mild situational anxiety (35 points) according to the Spielberger Anxiety Inventory. Based on the results of the neuropsychological examination, SCI was diagnosed.

General and biochemical blood tests, general urine analysis did not reveal any clinically significant changes. Vitamin B_{12} and folic acid levels are normal. MRI of the brain (February 2023) revealed minimal diffuse expansion of the subarachnoid spaces, score 1 according the Visual Rating of Medial Temporal Lobe Atrophy (MTA 1).

Long-term observation of the patient showed her anxiety about memory impairment, fluctuations in the severity of this anxiety, however, no changes were found in repeated neuropsychological studies. For example, after 4 years, the 12-Word Test: with immediate reproduction, 11 words were named and with a hint, one word (a total of 12 words), with delayed reproduction, 11 words were independently named and with a hint, one word (a total of 12 words). When assessing the emotional state, there are no signs of depression according to the Beck Depression Inventory (7 points), there is mild personal anxiety (39 points) and low situational anxiety (25 points) according to the Spielberger Anxiety Inventory.

The CSF was examined using electrochemiluminescence analysis (Roche Diagnostics on the Cobas e 601 analyzer in accordance with the approved methodology, which revealed no changes in biomarker values ($A\beta_{42}$ – 1542.00 pg/ml with the norm >1030 pg/ml), normal levels of total (132.5 pg/ml with the norm <300 pg/ml) and phosphorylated tau protein (11.3 pg/ml with the norm <27 pg/ml).

Thus, the patient has been showing no changes in CF during repeated neuropsychological examinations for a long time, and no significant brain damage according to MRI data, a pronounced accentuation regarding the presence of CI, and no positive biomarkers for AD. The patient's CI is likely to be functional in nature.

Management of patients with SCI

The basis for managing patients with SCI is non-drug methods. It is recommended to follow the rules of dementia prevention: quitting smoking and alcohol abuse, maintaining optimal blood pressure, effective treatment of diabetes mellitus (if present), maintaining normal body weight, high mental, social and everyday activity, regular physical activity, proper nutrition, effective treatment of mental and emotional disorders if present, maintaining normal sleep [25]. The most effective is a combination of all non-drug therapies, as shown by the results of long-term observation of elderly people [26], patients with SCI [27]. According to one of the latest meta-analyses, regular physical exercise more significantly reduces SCI than cognitive training [11].

In the last two years, anti-amyloid monoclonal antibodies aimed at preventing AD progression have begun to be used in the USA and some other countries [28]. Currently, the effectiveness of lecanemab in slowing the progression of AD at the stage of MCI and mild dementia has been proven [29]. Recently, data on the effectiveness of another anti-amyloid drug, donanemab, have been published [30]. The use of these drugs is recommended only at the stage of MCI and mild dementia due to AD, confirmed by the presence of biological markers of the disease [31]. If the patient has MCI, dynamic monitoring is recommended and, if progression occurs to the stage of MCI, the start of anti-amyloid therapy should be discussed. Many issues of the efficacy and safety of new expensive anti-amyloid drugs require further study, as well as their evaluation in real clinical practice [31, 32].

Thus, the use of biological markers of AD in the CSF allows to suggest an early (second) stage of AD in the cases of SCI or, conversely, to establish the functional nature of CI. The detection of the Alzheimer's nature of CI at the SCI stage indicates the need to monitor the patient and, in the case of progression of CI to the MCI stage, to discuss the advisability of using anti-amyloid therapy.

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