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DIFFERENTIAL DIAGNOSIS FEATURES OF RAPIDLY PROGRESSIVE ALZHEIMER'S DISEASE

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Introduction. The range of pathologies and conditions that can lead to the development of rapidly progressive dementia (RPD) is rather extensive. Alzheimer's disease (AD) is considered the most common cause of dementia. However, there are other pathologies that, unlike AD, are curable, and, given accurate diagnosis, allow a complete regression of pathological symptoms to be achieved. This highlights the importance of differential diagnosis of rapidly progressing AD from other causes of RPD.

Objective. To determine the differential features of rapidly progressing AD and to study the main causes predisposing to the development of RPD but not related to neurodegenerative pathology.

Discussion. Rapidly progressing AD differs from typical AD in the rate of cognitive decline. On average, rapidly progressing AD is associated with a loss of three points or more scores on the Mini-Mental State Examination (MMSE) test within six months and a faster (in 2–3 years) achievement of the terminal stage of the disease. In case of typical AD, this period is longer, lasting for about 8–10 years. Other major causes of RPD include prion diseases, neurodegenerative diseases of non-prion etiology (including rapidly progressing AD), vascular diseases, infectious diseases, inflammatory and autoimmune diseases, oncological diseases, metabolic and deficiency disorders, endocrine disorders, toxic and iatrogenic disorders, mental diseases, and cerebrovascular pathology.

Conclusions. Identification of the RPD cause requires a detailed and comprehensive examination of the patient using various laboratory and instrumental research methods, which is the key to accurate diagnosis and further successful drug correction of terminal diseases. Positron emission tomography of the brain and such biomarkers as beta-amyloid and hyperphosphorylated tau protein in the cerebrospinal fluid play a major role in the diagnosis of rapidly progressive AD and differential diagnosis from other RPD causes.

Keywords: rapidly progressing Alzheimer's disease; rapidly progressive dementia; cognitive impairment; differential diagnosis; cerebrovascular diseases; autoimmune encephalitis

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ОСОБЕННОСТИ ДИФФЕРЕНЦИАЛЬНОГО ДИАГНОЗА БЫСТРОПРОГРЕССИРУЮЩЕЙ БОЛЕЗНИ АЛЬЦГЕЙМЕРА

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Введение. Спектр патологий и состояний, которые могут приводить к развитию быстропрогрессирующей деменции (БПД), достаточно обширен. Наиболее распространенной причиной развития деменции является болезнь Альцгеймера (БА), однако существуют и другие патологии, которые, в отличие от БА, являются излечимыми, и при верной постановке диагноза возможно достижение полного регресса патологической симптоматики. Вышесказанное повышает значимость дифференциальной диагностики быстропрогрессирующей БА с другими причинами БПД.

Цель. Определить дифференциальные особенности быстропрогрессирующей БА и изучить основные причины, предрасполагающие к развитию БПД и не связанные с нейродегенеративной патологией.

Обсуждение. Быстропрогрессирующая БА отличается от типичной БА скоростью когнитивного снижения: в среднем при быстропрогрессирующей БА отмечается потеря 3-х баллов или более по Краткой шкале оценки психического статуса в течение шести месяцев и более быстрое (за 2–3 года) достижение терминальной стадии заболевания, в то время как при типичной БА этот период длительнее и составляет порядка 8–10 лет. К другим основным причинам БПД относятся прионные заболевания, нейродегенеративные заболевания неприонной этиологии (в том числе быстропрогрессирующая БА), сосудистые, инфекционные, воспалительные и аутоиммунные, онкологические заболевания, метаболические и дефицитарные нарушения, эндокринные расстройства, токсические и ятрогенные нарушения, психические заболевания, цереброваскулярная патология.

Выводы. Выявление причины БПД требует детального и всестороннего осмотра пациента с проведением различных лабораторных и инструментальных методов исследования, что является залогом верной постановки диагноза и дальнейшей успешной медикаментозной коррекции курабельных заболеваний. Основную роль в постановке диагноза быстропрогрессирующей БА и дифференциальной диагностике с другими причинами БПД играет позитронно-эмисионная томография головного мозга и уровень биомаркеров, таких как бета-амилоид и гиперфосфорилированный тау-протеин, в цереброспинальной жидкости.

Ключевые слова: быстропрогрессирующая болезнь Альцгеймера; быстрогрессирующая деменция; когнитивные нарушения; дифференциальная диагностика; цереброваскулярные заболевания; аутоиммунный энцефалит

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INTRODUCTION

Dementia is a global challenge for healthcare systems. Dementia is a neuropsychiatric syndrome characterized by a marked decrease in cognitive functions and the development of professional, household, and social maladaptation of the patient [1]. The World Health Organization (WHO) lists dementia as one of the most disabling diseases, the prevalence of which has recently been increasing worldwide [2].

The literature and statistical data confirms Alzheimer's disease (AD) to be the most common cause of dementia. However, typical AD refers to diseases characterized by a gradual progression of cognitive deficits. At the same time, there appear more diagnostic cases associated with a rapid progression of cognitive decline to the degree of dementia. These cases also include a large proportion of AD patients [3].

Although various authors identify prion diseases, Creutzfeldt-Jakob disease (CJD) in particular, as the most common etiology of rapidly progressive dementia (RPD) [4, 5], the current literature mentions other neurodegenerative diseases (nonprion), including AD, as the cause of RPD development. For example, a five-year comparative study [6] showed that neurodegenerative diseases of a nonprion etiology were the cause of RPD in 38% of cases, while prion diseases occurred in only 19% of cases. In addition to CJD and AD, the range of pathologies and conditions that can lead to the development of RPD is quite extensive (see Table).

At the same time, the importance of timely and accurate diagnosis is emphasized the possibility of a partial or complete elimination of cognitive impairment (CI) and other neurological symptoms in some pathologies that can lead to the development of RPD. In a two-year retrospective cohort study conducted in China, the authors [7] demonstrated that out of 310 patients hospitalized with RPD, 68 (21.9%) had viral encephalitis, followed by AD — 45 (14.5%) and autoimmune encephalitis — 28 (9.0%) patients. CJD was detected in only 22 (7.1%) patients. Another research group [8] published a prospective observational study, in which 86 (55.5%) of 155 patients with RPD had potentially treatable causes, such as autoimmune encephalitis (n = 52), vascular diseases (n = 14), neoplastic syndrome (n = 7), toxic/metabolic disorders (n = 7), psychiatric (n = 4), and other diseases (n = 12). The median age of the onset of RPD symptoms in that study was 68.9 years (ranging within 22.0–90.7 years). At the same time, the age of the onset of symptoms <50 years was one of the parameters that were most typical of patients with curable causes of RPD [8]. This indicates that some cases with a rapid progression of cognitive deficits are observed in young people of working age and, in the absence of timely treatment, may lead to professional disablement.

In the light of the above, research into the causes of RPD development is of particular importance. In this connection, our aim was to determine the differential features of rapidly progressing AD and to study the main causes predisposing to the development of RPD that are not related to neurodegenerative pathology.

Table. Causes of rapidly progressive dementia

Group	Deseases
Neurodegenerative diseases*	Prion diseases, rapidly progressive AD, rapidly progressive Lewy body dementia (LBD), frontotemporal dementia (FTD), progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, Huntington's disease
Cerebrovascular diseases	Multi-infarct dementia, stroke in areas strategic for cognitive functions, cerebral amyloid angiopathy, mitochondrial encephalopathy with stroke-like episodes and lactate acidosis (MELAS syndrome), CADASIL syndrome, CNS vasculitis, cerebroretinal microangiopathy with calcifications and cysts, posterior reversible encephalopathy syndrome, venous thrombosis
Infectious diseases	Meningitis and encephalitis of various etiologies (e.g., tuberculosis, herpes simplex virus, fungal), neurosyphilis, neuroborreliosis, HIV infection, progressive multifocal leukoencephalopathy, CNS toxoplasmosis, Whipple's disease
Inflammatory and autoimmune diseases	Autoimmune encephalitis, Hashimoto's encephalopathy, multiple sclerosis, acute multiple encephalomyelitis, neurosarcoidosis, celiac disease, autoimmune GFAP astrocytopathy
Cancers	Primary CNS tumors, CNS lymphoma, metastatic solid tumor, meningeal carcinomatosis, paraneoplastic syndrome
Metabolic and endocrine disorders	Hepatic encephalopathy, uremic encephalopathy, thyroid gland pathology associated with changes in thyroid-stimulating hormone levels, increased or decreased endocrine activity of the parathyroid glands, adrenal insufficiency
Deficiency disorders	Vitamin B deficiency (B_1, B_3, B_9, B_{12}), electrolyte disturbances, pellagra
Toxic and iatrogenic disorders	Degeneration of the nervous system caused by alcohol; poisoning with bismuth, mercury, lithium, arsenic, lead; neuroleptic malignant syndrome, serotonin syndrome
Mental illness	Psychotic disorders, depression, bipolar disorder, simulation disorder, conversion disorder

Table prepared by the authors using data from references [5–11]

Note: * — the group includes prion and nonprion neurodegenerative diseases; LBD — Lewy body dementia; MELAS — mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

MATERIALS AND METHODS

The scientific literature search was conducted using electronic bibliographic databases in the Russian (eLibrary, CyberLeninka) and English (Web of Science, Scopus, PubMed) languages. The search queries included the following keywords or phrases: rapidly progressive dementia; rapidly progressive Alzheimer's disease; cognitive impairment; differential diagnosis (in Russian); rapidly progressive Alzheimer's disease; rapidly progressive dementia; cognitive impairment; differential diagnosis (in English). The search depth was 10 years.

The inclusion criteria were systematic literature reviews and meta-analyses with information on the causes of RPD, rapidly progressive AD, and diagnostic methods used to identify the disease or condition underlying the development of RPD; original articles reporting the study of RPD causes. The exclusion criteria were theoretical models, theses, and conference materials.

RESULTS AND DISCUSSION

Characteristics of rapidly progressive dementia (RPD) and its underlying reasons

Most researchers refer to RPD as the development of cognitive decline and its rapid progression to the state of dementia over a relatively short period of time, lasting for several weeks or months and no more than two years in most cases [8–10]. However, it should be emphasized that there are no uniform criteria for RPD, with the information about RPD frequency and its main etiology being rather diverse.

Thus, prion diseases, neurodegenerative diseases of a nonprion etiology (including rapidly progressing AD), vascular diseases, infectious diseases, inflammatory and autoimmune diseases, oncological diseases, metabolic and deficiency disorders, endocrine disorders, toxic and iatrogenic disorders, and mental illnesses are distinguished among the main causes of RPD. The Table above shows the diseases and pathological conditions leading to RPD, which does not exclude the presence of other, rarer pathologies that may be the cause of its development [8–11].

The presence of a wide range of pathologies capable of causing the development of RPD dictates the need to differentiate rapidly progressing AD not only from CJD and neurodegenerative diseases (Lewy body dementia (LBD), frontotemporal dementia (FTD), corticobasal degeneration), but also from many other diseases. In this regard, the knowledge of medical professionals about rapidly progressing AD and its differential diagnosis from other significant etiologies of RPD, such as cerebrovascular pathology, infectious diseases, inflammatory and autoimmune diseases, requires elucidation.

AD as a underlying cause for RPD development

AD is a common neurodegenerative disease, which is believed to be among the main causes of dementia. Therefore, AD is to be considered in the differential diagnosis of RPD [12].

It should be noted that the clinical manifestations of AD can be different, depending on the time of the onset of the disease and its form. Thus, AD with the early onset (before the age of 65) differs from that with the late onset (after the age of 65). The guidelines of the International Working Group (IWG) as of 2014 distinguish the following forms of AD: typical, atypical (frontal variant of AD, logopenic variant of primary progressive aphasia syndrome, posterior cortical atrophy), and mixed [13].

The typical form of AD course, which can be referred to as classical, is characterized by slow progression. According to neuropsychological testing, cognitive functions demonstrate a decrease in the Mini-Mental State Examination scores (MMSE; normal levels of 28–30 scores) on average from two to four or more per year. After 8–10 years, this gradual deterioration leads to the terminal stage of the disease, i.e., severe dementia (10 or less MMSE scores) [14, 15]. However, AD may have another, rapidly-progressing form. Thus, the expert group [16] conducted a systematic review of 61 articles and published a consensus document, which proposed to use the loss of three or more score during the period of six months as an empirical definition of rapid cognitive decline and to apply this definition in routine medical practice for clinical decision making in patients with a mild to moderate severity of AD. At the same time, the achievement of the terminal stage (severe dementia) and disability of the patient with the loss of independence in RPD occurs much faster, on average, over 2–3 years.

According to [17], a significant proportion of patients may experience a rapid progression of AD. Thus, in a longitudinal two-year study, 686 patients with mild to moderate AD were observed. In this study, 30% of patients showed a decrease in cognitive functions by MMSE exceeding three scores per year, which was twice as fast as the average of the entire cohort. This demonstrates the high prevalence of this type of AD course.

In general, such factors as medical and social support for the patient, genetic predisposition, as well as concomitant cerebrovascular and other comorbid pathologies, especially at the stage of decompensation, may have an impact on the rate of AD progression. For example, the presence of a history of strokes and/or chronic cerebral ischemia (CCI) can significantly exacerbate the clinical manifestations of AD and lead to a faster loss of independence of the patient. In this case, the rate of disease progression was shown to be higher [17, 18].

However, it should be emphasized that in most cases, rapidly progressive AD occurs in patients under 65 years of age, i.e., with an early onset of the disease. AD is a disease that is frequently inherited. Thus, hereditary forms account for 10% of the total number of patients with AD (the remaining cases are sporadic). The presence of pathological genes is mainly noted in patients with the early onset of the disease (under 65 years of age).

Accordingly, it can be assumed that genetically-determined disorders that lead to early neuronal damage and synaptic dysfunction are among the main factors in the development of rapidly progressing AD. The study [18] observed a cohort of patients with rapidly progressing AD and found the frequency of the Apoliprotein E (*ApoE ε4*)

gene allele of 23.1%. *ApoE* is the most important genetic risk factor for sporadic AD, affecting the timing of the onset of the disease. It is assumed that the *ApoE* allele *ε4* gene is not widespread among patients with a rapidly progressive form of AD. Nevertheless, the question of whether the *ApoE* genotype is associated with the progression of AD is still a matter of debate [16].

Most researchers note the presence of severe amyloid angiopathy as a reason underlying the rapid progression of AD. This condition contributes to a faster damage to brain neurons, which is clinically manifested by a rapid decrease in cognitive functions [19, 20] compared with the classical form of AD development.

It should be noted that rapidly progressing AD is characterized by a diffuse brain damage, which primarily affects the cortical regions [21]. In this regard, the AD clinical picture, in addition to the presence of rapidly progressive cognitive impairments (CI), is characterized by other neurological symptoms, including motor disorders with damage to the pyramidal and extrapyramidal systems (to a greater extent) or emotional-volitional disorders [22]. According to [23], patients with rapidly progressing AD may have earlier behavioral and psychotic disorders, while the clinical manifestations of rapidly progressing AD may mimic CJD, which causes diagnostic difficulties.

One difficulty in establishing the diagnosis of rapidly progressing AD is associated with its highly diverse clinical picture. For this reason, changes in both neuroimaging and laboratory biomarkers can be used as distinctive differential features of rapidly progressing AD from RPD of another etiology. Positron emission tomography (PET) with beta-amyloid (Aβ) or tau protein (tau) ligands and PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) are among the most accurate neuroimaging diagnostics methods. At the same time, brain MRI in rapidly progressing AD does not have clearly specific signs. Given the lesion nature in rapidly progressive AD, neuroimaging analysis (brain MRI) shows diffuse atrophic changes that rapidly increase under dynamic observation. In the Russian Federation, PET with beta-amyloid (Aβ) ligands or tau protein (tau) remains, unfortunately, a poorly accessible diagnostic method, unlike PET with ^{18}F-FDG, which is also sensitive to changes in AD. The research team [24] noted that positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is capable of identifying regionally specific hypometabolism in the left angular gyrus and the left temporal cortex.

Currently, laboratory biomarkers play a leading role in the AD diagnosis, including rapidly progressing AD. These are biomarkers in biological fluids, with the most accurate diagnostic indicators being in cerebrospinal fluid (CSF): Aβ42, p-tau217, p-tau181, p-tau231, ratios of p-tau181/Aβ42, t-tau/Aβ42, and Aβ42/Aβ40. At the same time, low levels of Aβ42 in CSF, lower levels of the Aβ42/Aβ40 ratio, as well as increased indicators of the p-tau181/Aβ42 ratio may be associated with a faster decline in cognitive functions. In addition, patients with rapidly progressing AD showed higher levels of p-tau than patients with typical AD [22].

Blood plasma parameters in the AD diagnosis, including rapidly progressing AD, are also being actively studied. Thus, the longitudinal study [16], which included 122 patients with AD observed for an average of 4.2 (2.6) years, found a link between blood plasma biomarkers and the rate of disease progression. It was noted that lower levels of Aβ40 and Aβ42 were associated with a significantly faster cognitive decline.

Currently, no pathogenetic treatment for rapidly progressing AD, as well as for a typical form of AD, exists. Therefore, standard anti-dementia therapy aimed at slowing the progression of the disease is used. In rapidly progressing AD, an earlier transition to a combination therapy by cholinesterase inhibitor and memantine is recommended [25, 26].

Cerebrovascular pathology as a cause of RPD development

Cerebrovascular pathology, along with neurodegenerative diseases, is a common cause of severe cognitive dysfunction (dementia). Most vascular diseases of the brain, including multi-infarct dementia, strokes in strategic areas crucial for cognitive functions, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and vasculitis of the central nervous system (CNS), can cause the development of RPD [26].

It should be noted that in the first post-stroke year, more than half of patients develop CI. However, in the absence of other concomitant vascular, neurodegenerative, or somatic pathologies, the CI progression, as a rule, does not occur. On the contrary, there may be a positive trend against the background of ongoing rehabilitation measures. At the same time, in the presence of repeated strokes or comorbid pathology, a rapid cognitive decline may occur [27]. Secondary post-stroke complications, such as seizures, can also accelerate the CI progression.

An important role in the RPD development is played by the stroke in strategic areas crucial for cognitive functions, which include the thalamus, angular gyrus, caudate nucleus, limbic system, prefrontal cortex, and medial temporal lobes. Thus, when the thalamus is affected, depending on the circulatory disorders of a particular artery, as well as the side of the lesion, various disorders may be observed: decreased memory for current events (both auditory and visual), impaired orientation in time, aphasia, akinetic mutism, impaired counting, impaired regulatory functions, neglect syndrome, impaired constructive practice, neuropsychiatric symptoms, and other neurological symptoms (e.g., oculomotor disorders) [28].

Stroke treatment depends on its type and includes not only specific therapy, but also secondary stroke prevention (correction of the main risk factors) and rehabilitation measures. It should be noted that a possible complete or partial regression of symptoms will depend on the stroke severity, lesion location, adequate therapy, proper prevention of post-stroke complications, and rehabilitation of the patient [27, 28].

The syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

(CADASIL) can also underlie the RPD development. CADASIL is the most common hereditary disease of small cerebral vessels characterized by non-atherosclerotic and non-amyloid diffuse angiopathy with predominant lesion of small and medium penetrating and leptomeningeal arteries [29]. Clinically, this arteriopathy is manifested by migraine with aura, recurrent subcortical ischemic strokes, and/or stroke-like episodes, affective disorders, and CI. Cognitive dysfunction in this disease is detected in about 50% of patients. It is a progressive subcortical type of dementia. Moderate CI, including impairment of executive functions, memory, and attention, occur in patients long before the onset of subcortical ischemic events [29, 30].

Magnetic resonance imaging (MRI) of the brain in patients with CADASIL usually reveals bilateral symmetrical diffuse leukoareosis, accompanied by multiple lacunar infarcts in the subcortical and periventricular white matter, basal ganglia on both sides. A characteristic manifestation of CADASIL is hyperintensivity in the T2/FLAIR mode in the pole of the temporal lobe, the outer capsule and the corpus callosum [30]. Currently, genetic testing is considered the leading method of identification and diagnosis of CADASIL. Mutations of the *NOTCH3* gene, as well as, in more rare cases, the *Arg332Cys* gene, cause the disease development [30].

Currently, no treatment with proven efficacy has been developed; thus, symptomatic therapy and strategies for managing vascular risk factors are used. In some studies [31], executive function improvements were noted when taking donepezil; however, the clinical significance of these results remains unclear, requiring further confirmation.

In primary CNS vasculitis, most patients exhibit the signs of acute CNS, which progress rapidly during the period from two weeks to 12 months. These signs often include headache, motor deficiency (hemiparesis), speech disorders (aphasia), seizures, visual disturbances, and symptoms associated with spinal cord injury. Strokes, if they develop, are usually multiple and bilateral. Depending on the clinical picture, it is possible to indirectly judge which vessels are affected. In the case of damage to large-caliber vessels, symptoms similar to stroke and focal neurological symptoms prevail. In the case of damage to small blood vessels, symptoms associated with impaired cognitive functions and epileptic seizures are more common. In vasculitis-caused dementia, cephalgic syndrome is somewhat more common than in other types of dementia. Another feature is the faster progression of cognitive impairments (RPD): not years, as in dementias of primary degenerative origin, but months or even weeks. At the same time, the nature of neurological disorders depends on the area that is affected, and signs of systemic disease may be absent [32].

The differential diagnosis of primary vasculitis should exclude infectious, malignant or systemic inflammatory diseases, as well as reversible cerebral vasoconstriction syndrome. Typical MR signs of the disease are multifocal bilateral foci in the T2 or FLAIR mode in the cortical and subcortical regions, as well as in deep white and gray matter (basal ganglia). CT or MR angiography is used to refine the imaging picture. This method allows detecting changes mainly in large blood vessels in the form of thickening of the walls and intrahepatic post-contrast edema as a sign of active vasculitis. When the lesion is localized mainly in the distal parts (small vessels) and in the posterior cerebral artery system, cerebral angiography is a more sensitive method. At the same time, the gold standard diagnostics comprises a brain biopsy with histological verification [33].

The remission possibility in primary vasculitis underscores the importance of differential diagnostics of RPD. The corresponding treatment includes corticosteroids and/or cytostatics (usually cyclophosphamide) with the therapy being continued for 6–12 months after achieving remission [34, 35].

Infectious diseases as etiological factors in RPD development

Infectious diseases are among the most common causes of RPD, with their prevalence over other causes of rapidly progressive cognitive deficits being confirmed [7]. This observation was likely related to the inclusion of younger patients in these studies, among whom infectious and inflammatory diseases are much more common than neurodegenerative pathologies. Bacterial, viral, fungal, and protozoan brain infections leading to the development of dementia are well known; the relevant data are presented in the Table. In most cases, infections with CNS damage are characterized by an acute onset; however, there are forms with a subacute and chronic course [36].

Establishing the diagnosis of encephalitis caused by an infectious disease in the acute period can be difficult, since the clinical symptoms are nonspecific and may either include various neurological manifestations or not include them at all (in the abortive form). It should be noted that patients with infectious diseases are characterized not only by neurological symptoms (meningeal cerebral and focal neurological symptoms), but also by a general infectious syndrome (hypertemia, changes in peripheral blood, skin rashes, tachycardia, tachypnea and other manifestations) [37]. Other organs and systems may also be affected. For example, Whipple's disease, a rare infectious disease, which can cause the development of RPD, is associated with damage to several systems: gastrointestinal, respiratory, cardiovascular, nervous, as well as eyes and joints. The main neurological manifestations are dementia, supranuclear ophthalmoplegia, and myoclonus [37].

It should be noted that an infectious disease as the primary cause of dementia is usually considered as a diagnosis of exclusion. The cognitive decline in infectious diseases is not the sole neurological symptom, which may progress rapidly. This makes it possible to suspect an infectious lesion of the central nervous system and require a lumbar puncture followed by cerebrospinal fluid (CSF) examination and the exclusion of a potentially reversible infectious process. However, in the early stages of infectious diseases,

CSF analysis alone is insufficient for diagnosis, which requires additional research methods, such as brain MRI, electroencephalography (EEG), electroneuromyography (ENMG), etc. [36].

Treatment for RPD in such cases depends on the etiology of the infectious disease and may include antiviral, antibacterial, and other medications directed against infectious agents. It is important to emphasize the probability of a favorable outcome of the disease with a regression of symptoms, including CI, given that the infectious origin of RPD is confirmed and adequate treatment is initiated in a timely manner.

Inflammatory and autoimmune diseases as a cause of RPD development

Although RPD was first mentioned in patients with multiple sclerosis (MS), demyelinating inflammatory diseases such as MS and acute multiple encephalomyelitis rarely trigger RPD. In this group, autoimmune encephalitis (AE) is the most common cause of RPD [38].

AE is a heterogeneous group of immune-mediated paraneoplastic and nonparaneoplastic (idiopathic) encephalitis, which leads to the development of encephalopathy. Given the multifocal brain lesion, the clinic picture may be diverse. Cognitive, emotional, and mental disorders such as behavioral disorders (aggression, irritability), depressive symptoms, anxiety, obsessive-compulsive symptoms, hallucinations, subacute dementia, anterograde amnesia and others, which result from the damage to the structures of the limbic system (limbic encephalitis), also list cerebellar degeneration, Bickerstaff's disease, and epileptic seizures. Chorea involving the facial muscles or atypical Parkinsonism syndrome may also occur. Anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis is the most studied and widespread among AE, which plays an important role in the development of RPD [38].

Anti-NMDA receptor encephalitis affects mainly young people (95% of patients under 45 years of age); the disease is more common among females (80% of women). The relationship of AE development with the presence of ovarian teratoma is revealed in more than half of female patients [39]. Anti-NMDA receptor encephalitis is characterized by a nonspecific flu-like prodrome, after which neuropsychiatric symptoms develop acutely in some cases. The most common symptoms of mental disorders are emotional lability, anxiety, fears, insomnia, manic state, delusions, and hallucinations. In this regard, about 60% of patients are initially admitted to psychiatric clinics. The majority of patients also experience rapidly progressive CI, in which episodic memory and regulatory functions are affected. Somewhat later, extrapyramidal disorders (dystonia, chorea, or stereotypy), catatonia, and autonomic dysfunction join. However, in clinical practice, the appearance of extrapyramidal disorders and catatonia is often regarded as the consequences of antipsychotic therapy, which is prescribed to patients taking into account the presence of neuropsychiatric disorders. This may lead to diagnostic errors. Almost 85% of patients develop epileptic seizures, which frequently remain unrecognized due to extrapyramidal symptoms, psychomotor agitation, or the need to maintain drug sedation. Overall, the clinical picture demonstrates the complexity of overlapping psychiatric and neurological symptoms and highlights the need for an interdisciplinary approach to diagnosis and treatment [40, 41].

To confirm the diagnosis, it is necessary to determine the titer of antibodies to NMDA receptors in biological fluids such as blood or CSF. Only about 50% of patients exhibit brain MRI changes, such as T2/FLAIR hyperintensivity areas in the hippocampus, cerebral cortex, cerebellar hemispheres, insula, fronto-basal region, basal ganglia, and brain stem. In the event that the brain MRI reveals no changes, patients undergo an additional study by positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG). This study determines the frontal-temporal-occipital gradient of glucose metabolism, which correlates with the activity of the disease. The EEG may reveal a specific pattern of extreme delta brushes, i.e., a rhythmic δ-activity with a frequency of 1–3 Hz with bursts of rhythmic β-activity superimposed on each δ-wave, resembling δ-brushes in premature infants. This phenomenon occurs in almost 30% of cases of anti-NMDA receptor encephalitis [11, 40].

It should be noted that in about 70% of patients, timely treatment of anti-NMDA receptor encephalitis results in complete or almost complete regression of symptoms. There are three lines of therapy:

1. Pulse therapy with glucocorticosteroids and/or immunoglobulin intravenously, plasmapheresis;
2. Rituximab or cyclophosphamide or a combination thereof;
3. Other cytostatic immunosuppressants.

In case of ineffectiveness of first-line therapy, the drugs of the following lines are prescribed. Together with the therapy, a diagnostic search for oncological diseases is carried out and, if necessary, antitumor therapy is performed [9, 11].

Hashimoto's encephalopathy (HE) may be another cause of RPD development in this group of diseases. HE is a rare autoimmune disease known as steroid-reactive encephalopathy associated with autoimmune thyroiditis. HE is more common among women (70–85% of cases). At the same time, the clinical picture of HE includes various neurological and psychiatric symptoms, the variety of which complicates its timely diagnosis. Among the neurological symptoms, the most common are extrapyramidal symptoms, ataxia, epileptic seizures, transient aphasia, rapidly progressive cognitive decline to dementia, and confusion. There may even be stroke-like episodes. Patients also experience behavioral disorders and visual hallucinations. A rapid increase in the symptoms of the disease and a fluctuating course are characteristic [42].

In order to confirm the HE diagnosis, the necessary criterion involves the detection of a high titer of antithyroid antibodies (antibodies to thyroglobulin and antibodies to thyroperoxidase) in the blood and the absence of other causes of brain damage that could better explain the clinical picture. Patients with HE may have hypothyroidism,

hyperthyroidism, or euthyroidism; therefore, assessment of thyroid hormone levels does not have a diagnostic significance in HE detection. The results of CSF analysis and brain MRI scans do not reveal any specific changes. Thus, in patients with HE, there is only an increase in the level of protein in the CSF, and according to brain MRI, half of the patients have nonspecific changes in subcortical white matter and cerebral atrophy. Intermittent slow-wave activity and three-phase waves are most often observed in the EEG during HE. HE is a curable disease. In most cases, the symptoms regress after the use of immunosuppressive therapy. The first-line drugs are glucocorticosteroids. With timely and accurate diagnosis and well-selected therapy, the prognosis after treatment of the disease is favorable [43].

CONCLUSION

Although RPD accounts for only about 3–4% of dementia cases, it is a disproportionately large clinical problem due to the need for a broad differential diagnosis, a variety of possible diagnostic tests, and the need to complete the assessment at a pace consistent with the rate of cognitive decline. The existing extensive list of pathologies associated with the onset of rapidly progressive cognitive deficits and the presence of potentially curable diseases highlights the importance of further research in this direction.

Given the presence of such a wide range of diseases, the approach to the differential diagnosis of rapidly progressing AD should include a thorough medical history and physical examination, mandatory neuropsychological testing, and high-quality laboratory and instrumental diagnostics. PET scans of the brain and the study of AD biomarkers in the CSF are of the greatest importance in the differential diagnosis of rapidly progressing AD.

The study of other causes of RPD that are not related to neurodegenerative processes will make it possible to identify curable diseases. This indicates the need to increase the knowledge of medical professionals about the differential diagnosis of RPD.

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