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СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О КЛИНИКЕ И ДИАГНОСТИКЕ ПЕРВИЧНОГО ВАСКУЛИТА ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

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Modern Concepts on the Clinic and Diagnosis of Primary Vasculitis of the Central Nervous System

Резюме

Первичный васкулит центральной нервной системы (ПВЦНС) — редкая форма васкулита неизвестной причины, поражающего сосуды головного, спинного мозга и мозговых оболочек без системного поражения. Установлено, что средний возраст начала заболевания приходится на 50 лет. Клинические проявления зависят от калибра пораженных сосудов. Наиболее частыми начальными симптомами являются головная боль и сосудистые когнитивные нарушения, что связано с поражением сосудов малого калибра. Развитие инсульта и очаговых симптомов взаимосвязано с сосудистыми когнитивными нарушениями и проявляется поражением средних/крупных мозговых артерий. Диагностика ПВЦНС затруднена, так как симптомы васкулита за пределами центральной нервной системы встречаются редко, серологические маркеры воспаления находятся в норме. Анализ спинномозговой жидкости обычно не соответствует норме из-за умеренного неспецифического повышения уровня общего белка или количества лейкоцитов. У 97 % пациентов с ПВЦНС выявляются отклонения от нормы (инфаркты, иногда опухолевидные поражения) по данным магнитно-резонансной томографии головного мозга. Ангиография имеет низкую чувствительность и низкую специфичность, так как позволяет верифицировать васкулит только средних и крупных церебральных артерий, выявляя сегментарные сужения. Для выявления воспаления кровеносных сосудов, а также для исключения других заболеваний необходимо выполнить биопсию вещества и мягких оболочек мозга.

Ключевые слова: *первичный васкулит центральной нервной системы, сосудистые когнитивные нарушения, головная боль, нейровизуализация, биопсия*

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Abstract

Primary vasculitis of the central nervous system (PACNS) is a rare form of unknown cause vasculitis that affects the vessels of the brain, spinal cord and meninges without systemic damage. It was found that the average age of the onset of the disease was 50 years. Clinical manifestations depend on the caliber of the affected vessels. The most common initial symptoms are headache and vascular cognitive impairment associated with small vessel involvement. The development of stroke and focal symptoms is interrelated with vascular cognitive impairment and manifests as the lesion of the middle/large cerebral arteries. PACNS is difficult to diagnose, since symptoms of vasculitis outside the central nervous system are rare, serologic markers of inflammation are normal. The analysis of cerebrospinal fluid is usually abnormal due to a moderate nonspecific increase in the level of total protein or the number of leukocytes. Deviations from the norm (cerebral infarction, sometimes tumor-like lesions) are detected according to the data of magnetic resonance imaging of the brain in 97 % of patients with PACNS. Angiography has low sensitivity and low specificity, since it allows to verify vasculitis of only middle and large cerebral arteries, revealing segmental narrowing. To detect inflammation of the blood vessels, as well as to exclude other diseases, it is necessary to perform a biopsy of the substance and the soft membranes of the brain.

Key words: *primary vasculitis of the central nervous system, vascular cognitive impairment, headache, neuroimaging, biopsy*

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ANCA — antineutrophil cytoplasmic antibody, DC — dendritic cells, MRA — magnetic resonance angiography, MRI — magnetic resonance imaging, CTA — computer angiography, PCNSV — primary isolated central nervous system vasculitides (angitis), RCVS — reversible cerebral vasoconstriction syndrome, ERS — erythrocyte sedimentation rate, CAA — cerebral amyloid angiopathy, CNS — central nervous system, CSF — cerebrospinal fluid

Introduction

Vasculitides is a heterogeneous group of diseases caused by an autoimmune vessel injury, characterised by vessel wall inflammation, necrosis, deformation and sclerosis, resuling in ischemic changes in organs and tissues, the blood to which is supplied by damaged vessels. These diseases is a rare pathology: the annual incidence is appoximately 4.2 cases per 100,000 people; however, the number of cases tends to grow globally. Vasculitides can be primary (the cause is unknown) and secondary (caused by infections, cancer and rheumatoid diseases). Currently, the Russian Federation does not operate any unified register of patients with this disease [1-9].

The nomenclature and classification of vasculitides were discussed by leading experts during the Chapel Hill Consensus Conference (CHCC) back in 1992. The first classification based on the vessel size was successfully used over two decades. Along with emergence of new knowledge and achievements in dynamically developing field of rheumatology, a new, up-to-date classification was needed. In 2010–2011, leading experts were discussing classification of vasculitides with the help of highly experienced clinicians (GPs, rheumatologists, nephrologists, immunologists) and anatomic pathologists, from over 50 leading medical centers in Europe, America, Australia, China, and Japan. Thus, the most complete new information on existing vasculitides was presented in the vasculitides nomenclature during the 2012 Chapel Hill Consensus Conference (CHCC2012) [5-8]. The Chapel Hill nomenclature is erroneously called a classification, since it does not contain diagnostic criteria; it contains information on various forms of vasculitides based on the diameter of an affected vessel (large, medium-size and small vessels), etiology and patogenetic features of the inflammatory process, that is why it is quite bulky and is not handy for everyday use in clinical practice [5-7].

The main objective of the nomenclature is to develop a unified interdisciplinary approach, to classify available information of the diseases. Taking into account available data on the practical use of the terms and the idea of disease manifestations, the name was reviewed, and main categories were isolated. For the first time this up-to-date nomenclature was updated with a new additional category of variable vasculitides affecting vessels of any size and type; vasculitides of a single organ was included into a separate category. This category included cutaneous leukocytoclastic angitis, cutaneous arteritis, primary central nervous system vasculitides (PCNSV), isolated aortitis (there are no signs of the possibility of a limited systemic variant) [5-8].

Early diagnosis of vasculitides is challenging because of non-specific initial presentations and numerous symptoms resembling other diseases (clinical masking symptoms) [9, 10]. For a majority of clinical entities of vasculitides, there are no specific laboratory tests or diagnostic methods for antibody-negative vasculitides; therefore, it is recommended that the disease is diagnosed with biopsy and pathomorphological examination of biopsy material; instrumental diagnostic tools

(cerebral angiography, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and computer angiography (CTA), high-resolution MRI (HR-MRI) [9, 11] can be used as well.

Something that seemed impossible several years ago has become available due to development of new instrumental diagnostic methods that can not only identify, but also describe the progress of a number of vasculitides (Takayasu disease, Kussmaul disease, etc.) [10]. A rare, hard-to-diagnose, severe single-organ vasculitides is primary central nervous system vasculitides (PCNSV) [1-4, 8, 9, 12, 13]. Depression in patients with PCNSV increases the near-term risk of death and possible suicide, deteriorates cognitive functions and the quality of life, reduces functional activity, hinders rehabilitation and recovery [12-14]. A large study by Hajj-Ali R.A. et al. (2019) assessed the long-term capabilities, quality of life and depression in patients (n = 27) with PCNSV during 5.5 ± 4.7 years, using Barthel Index (BI), European Quality of Life Questionnaire (EuroQol) and Patient Health Questionnaire, PHQ-9. The analysis demonstrated that 19 patients out of 27 were mildly disabled (70.4 %), while 5 patients had severe disability (18.5 %). 14 patients out of 27 (51.9 %) did not have any problems with independent movement, 18 patients (66.7 %) could cater for themselves, and 15 patients (55.6 %) did not experience any limitations in their daily life. Only 8 patients (29.6 %) in the study group did not have concerns, while 70 % showed minor signs of depression [14]. In the study by C. Salvarani et al. (2015) conducted over a 29-year period (from 1983 to 2011), the PCNSV mortality was observed in 25 patients (15 %) out of 163. Without therapy, patients with PCNSV died within a year, any subsequent recurrence increased the risk of death [15].

PCNSV affects vessels of any size in the brain, rarely spinal cord, and their lining, while vessels in other organs and systems remain intact. In scientific medical literature, the abbreviation "PCNSV" is also used for the following diseases: primary central nervous system (CNS) angitis, isolated CNS vasculitides (angitis) [12, 13, 16-18]. Despite the fact that over the last decade this clinical entity gained attention, it still rare and understudied.

Epidemiology

It is hard to determine the exact incidence of PCNSV in the population, since the disease has no specific clinical manifestations, specific serum inflammatory markers, while neuroimaging diagnostic methods return false-positive and/or false-negative results; there are no generally accepted international standards for prompt PCNSV diagnosis [8, 15-20].

PCNSV is one of the rarest forms of vasculitides, with the assumed incidence being 2.4 cases per 1 million people. In the 17-year-long study by Salvarani C., et al. (2017), PCNSV was diagnosed in 64 % of cases in the group of 114 patients vs. CNS disorders associated with other types of vasculitides or other rheumatic conditions [21]. The mean age of disease onset is approximately 50 years; however, PCNSV can develop in any age [21]. Usually PCNSV is described as a disease affecting middle-age men. Bernstein J.E. et al. (2020) found that PCNSV affects men of 40–60 years old [21]. In the study by Sundaram S. et al. (2019), the mean age of 45 patients (68.9 % were men) was 36 years [23]. However, according to the study by Salvarani C. et al. (2017), the retrospective analysis of a group of 163 PCNSV patients who were followed up by Mayo Clinic (Rochester, Minnesota, USA) during 29 years, demonstrated that women prevailed (n = 86, 56 %) [21]. This form of vasculitides is observed in paediatric population as well. Elbers J. et al. (2016) described PCNSV in boys (62–74 %) [24].

Etiology and Pathogenesis

Causes and mechanisms of PCNSV are understudied; however, it is well known that vessel wall inflammation is facilitated by genetic factors and infections (varicella-zoster virus, Epstein-Barr virus, versatile virus west nile virus, human immunodeficiency virus). These etiologic factors are merely triggers, i.e., they trigger the pathological pocess. Unfortunately, genetic factors have not been studied systematically; there are no evidences of hereditary disease, and reliable causes of PCNSV are still unclear [1, 8-9, 11-13, 16-20, 24].

Epidemiological factors trigger autoimmune pathogenetic mechanisms of PCNSV, associated with immune system activation and inflow of activated macrophages and T-cell (mainly T-helpers), that reinforce the immune response, to the vessel wall. Self-sustained failure of tolerance to vascular cells occurs, and an immune response develops against native components (autoimmune antigens), that serve as a target for T-effector cells, causing damage to the vessel cells containing these autoimmune antigens. The area of vascular damage contains numerous T-effector cytokines, that affect the functional activity of vessel cells and apoptosis — programmed cell death.

Vasculitides is caused by impaired cell-mediated immunity (development of delayed hypersensitivity reaction). Numerous scientific papers describe migration of macrophages and effector T-lymphocytes that form granulomas (macrophages surrounded by T-lymphocytes). In turn, active macrophages cause vessel wall degradation, thus intensifying the pro-inflammatory

activity of endothelium and leading to hyperplasia and lymphocytic infiltration of endothelial cells. All these pathological changes result in granulomatous inflammation and, later, necrotising angiitis [1, 8-9, 11-13, 16-20, 24]. Vessel wall intima which is not hyperplastic and fibrotic, causes vessel lumen to narrow; a new vascular tree appears and occlusion occurs, thus causing damage to the vessel wall and hemorrhage into adjacent tissues [1, 8-9, 11-13, 16-20, 24].

Diagnostic Criteria and Clinical Presentation of PCNSV

First criteria for a differential diagnosis of PCNSV were proposed and developed for small arteries in 1988 by Americal rheumatologists Calabrese L. and Mallek J. In order to diagnose PCNSV, all three criteria below need to be met:

1) " Neurologic impairment or mental deterioration that cannot be explained by any other causes"
2) " Typical angiographic signs (alternating areas of gradual artery dilatation or narrowing) or histopathologycal manifestations in the CNS"
3) "No signs of widespread vasculitis and other diseases that can cause symptoms or angiographic signs of vasculitides" [1, 8, 25, 26].

Late in the XX century, Calabrese L., Mallek J. introduced the term "reversible cerebral vasoconstriction syndrome" (RCVS), which has clinical and angiographic signs (alternating areas of vessel dilatation or narrowing) similar to signs of PCNSV. However, this condition is caused by an idiopathic vasospasm and not by intracranial vasculitides. Unlike PCNSV, this syndrome is benign and has good prognosis [8, 25, 26].

It is worth mentioning that introduction of angiography into clinical practice allowed diagnosing and differentiating vasculitides depending on the size of an affected vessel. However, angiography is useful for vasculitides of large and medium-sized arteries, while vasculitides of small arteries remain negative and can be verified only with contrast angiography [8, 13, 16, 26].

In 2005–2010, when brain imaging diagnostic methods (high-resolution MRI) were developed for vasculitides verification, inflammation could be identified by thickening and contrast enhancement of the artery wall.

When the informative value of MRI as a method for PCNSV diagnosis was analysed, it became obvious that this method was not less superior than histology in terms of the following criteria: sensitivity and specificity (80 and 100 %, respectively) [8, 13, 16, 26].

In 2009 Birnbaum J. and Hellmann D. proposed to differentiate between confirmed (a histological examination of a tissue biopsy sample) and possible PCNSV in the absence of biopsy, when the signs of vasculitides were found on an angiocardiogram, together with abnormal MRI scans and cerebrospinal fluid (CSF) results that correlated with inflammation [27].

The modern medicine uses diagnostic criteria for vasculitides of small arteries which were developed 30 years ago by a group of scientists led by Calabrese L. and Mallek J [25], for any vessel size. PCNSV does not have a pathognomonic clinical presentation. In the first large study by Sarti C. et al. (2020), which was a detailed overview of all available literature sources on PCNSV, the authors summarised all medical records (n = 585) published in the medical database of the US National Library of Medicine (2002–2019) and analysed the clinical findings [26]. They found out that, depending on the brain areas involved, PCNSV can present with various clinical symptoms (Figure 1). Sometimes, the onset of the disease can be epileptic seizures [26].

Moreover, the disease severity and the rate of progression can differ a lot, thus enhancing the non-specific nature of clinical manifestations. A majority of patients had several symptoms and syndroms at a time [8, 21, 28-31].

Clinical symptoms depend on a various degree of pathology of the brain, or spinal cord, or meningeal layer: reduced lumen (stenosis or occlusion); segmental increase or decrease in the vessel diameter; formation of aneurysms with subsequent vessel wall rupture and hemorrhage into adjacent structures [8, 13, 16, 17, 26, 28].

The severity of the above symptoms depends on the diameter of the affected vessel. Very often cognitive disorders can be a first sign of PCNSV. More marked cognitive disorders are typical of PCNSV with small vessel involvement [8, 21, 29].

Salvarani C et al. (2017) and de Boysson H. et al. (2017) draw attention to the fact that in small artery vasculitides, vascular cognitive disorders are by 67–71 % more frequent and by 36–47 % more severe vs. involvement of large and medium-sized arteries. It was found out that vascular cognitive disorders in patients with PCNSV progressed within a month, sometimes within a week [21, 29]. In the study by Sundaram S. et al. (2021), where 45 patients with suspected PCNSV were examined, 19 patients had their diagnosis confirmed with high-resolution vessel wall imaging (HRVWI). Images evaluation revealed involvement of large (n = 13), medium-sized (n = 16), and small (n = 11) vessels, while cognitive impairment was observed in 5 patients (25 %) and was considered a poor prognosis [32].

In patients with PCNSV, cognitive disorders are often accompanied by mental and affective disorders: emotional instability, aggression, irritability, misinterpretation of own and other peoples' actions, sudden abandonment of an activity, confusion [33].

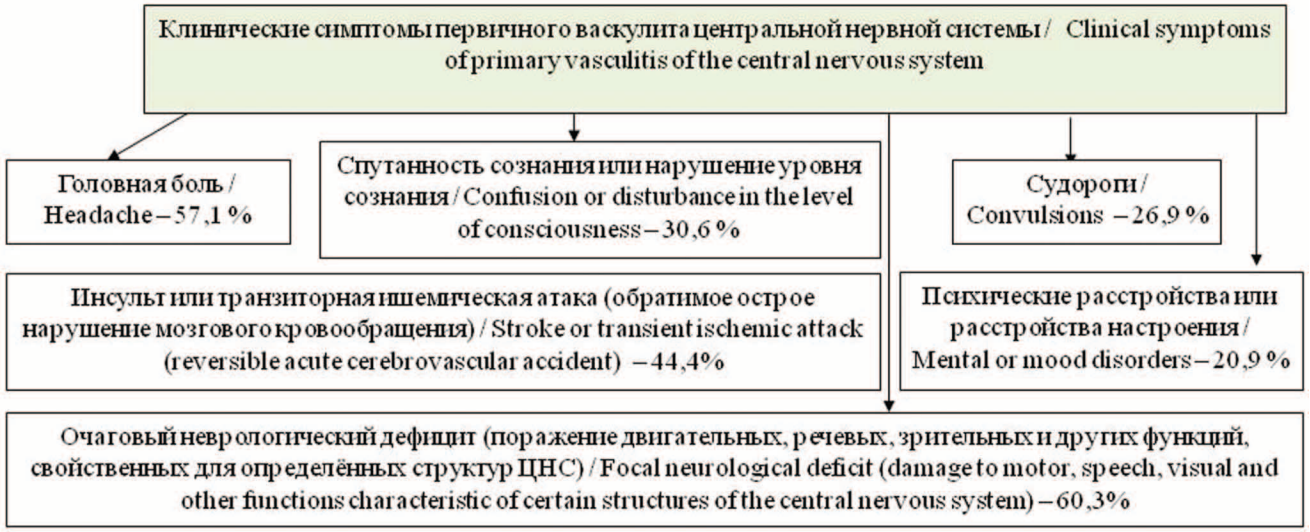

Figure 1. *Main clinical symptoms PVCNS*

The article by de Boysson H. et al. (2017) studied and compared clinical features of PCNSV in 102 patients. 26 patients (25 %) presented with isolated involvement of small vessels, 76 patients (75 %) had damage to their medium-sized/large vessels [29]. It was found out that small artery PCNSV is observed more frequently at a young age (41.5 years old) compared to medium-sized/large vessel PCNSV (48.5 years old), p = 0.04 [29]. 46 patients (45 %) had speech pathology, 22 patients (22 %) had mental disorders [29].

It was noted that in isolated small vessel involvement, as opposed to the involvement of medium-sized/large vessels, the following clinical symptoms were more common: epileptic seizures (n = 20; 77 %) vs. (n = 16; 21 %), p < 0,0001, dyskinesia (n = 9; 35 %) vs. (n = 7; 9 %) p = 0,002. In turn, where medium-sized/large vessels were damaged, 67 patients (88 %) had focal neurologic impairment: palsy, sensory or atrophic disorders (p = 0.0002), 64 patients (84 %) had stroke (p < 0.0001), 16 patients (21 %) suffered from insomnia (p = 0.03), 11 patients (42 %) had dizziness (p = 0.07) [29]. Headaches were observed in patients with damages to vessels of any size. Therefore, since headache (51–65 %) is one of the most common complaints in general and can be a sign of a number of neurological disorders, the features of headache which can help in suspecting PCNSV should be taken into account. Investigators often describe headache as subacute or chronic headache that starts unnoted; it is dull, diffuse, sometimes intermittent, intensifies with time, sometimes resembles migraine, or varies in severity, usually mild to moderate [34, 35]. Patients who already have headaches describes it as something different from the pain they used to have. In turn, in rare tumour-like PCNSV (5 %, mean age: 37 years old) caused by damage to small vessels, headache can be acute, severe and can be accompanied by vomiting and neurological disorders (epileptic seizures in 90 %) [26, 34, 36]. Clinical manifestations are a result of edema that presses the structures adjacent to the brain. Very often this form of PCNSV is confused with a tumour or lymphoma, therefore, prompt diagnosis of tumour-like PCNSV is difficult. Thunderclap headache is rarely observed in patients with PCNSV, and it helps differentiating it from other neurological disorders that can resemble its clinical presentation, for instance subarachnoid haemorrhage or reversible cerebral vasoconstriction syndrome [25, 26, 34, 37].

According to N.A. Totolyan et al. (2013), the diagnostic value of the clinical manifestations of PCNSV was considered in the following categories: headache (especially persistent, atypical, with meningeal or hypertensive manifestations, with specific onset time) — very high value (+++); step-wise progressing multifocal (mainly subcortical) neurological dysfunction syndrome, including cognitive disorders, disrupted innervation, pseudobulbar syndrome, bilateral pyramidal-extrapyramidal dysfunction with gait disturbance, pelvic disorders — high value (++) [9].

In the clinical practice, there are the following rare PCNSV variants: isolated spinal vasculitides (with frequent thoracic section involvement, 5 %), vasculitides with signs of hemorrhage, vasculitides with amyloid deposits [20, 38, 39, 40]. It is worth mentioning that the elderly patients (mean age: 65 years old) have this pathological peptide depositing in small arteries of the cortex, in the arteries of the meninx vasculosa and meninx serosa with the immune response to beta amyloid.

Table 1. The course of PPCNS depending on the caliber of the affected vessel

Small arteries	Large arteries
Progressive, long severe course	Monophasic, with the development of a fatality

Patients with this condition demonstrate high incidence of cognitive disorders (71 %) and a high risk of parenchymatous hemorrhage (20 %) [38, 39, 40]. The course of PCNSV depends on the size of a damaged vessel (Table 1).

According to de Boysson H et al. (2018), 10 % of patients with PCNSV had an instant poor course of the disease represented by impaired wakefulness and development of respiratory disorders (shortness of breath) [20].

Rarely there can be common symptoms evidencing a multisystem disease, such as fever (14 %), weight loss, rash, peripheral neuropathy, arthritis, and night sweats that were observed in 20 % of patients [15, 29]. Where these symptoms are present, secondary CNS vasculitides needs to be ruled out.

Diagnostic Features

Diagnostics is based on the above criteria (Calabrese L. and Mallek J., 1988) [25]. Irrespective of the achivements in the studies of PCNSV, making diagnosis is challenging due to the lack of highly sensitive and specific diagnostic tests. Laboratory tests, brain imaging and histopathology are useful methods both for confirmation of suspected PCNSV and for ruling out of other conditions with similar manifestations [1, 8-9, 11-13, 16-20, 24].

Laboratory Diagnostics

Usually, laboratory test values are within the reference range. In some cases, blood tests can demonstrate signs of system inflammation: anemia, leucocytosis, high platelet count, high ESR [33, 41]. 27-33 % of patients have increased acute phase protein (C-reactive protein) pointing out to an inflammation [33, 41]. In rare occasions, patients present with a diagnostically insignificant increase in specific blood markers: cytoplasmic antibodies (ANCA) and antinuclear antibody (autoimmune antibody that can damage the wall of small vessels) [8, 14, 42].

Cerebrospinal fluid (CSF) demonstrates abnormalities in 80–90 % of patients. According to Salvarani C. et al. (2015), an increased protein concentration is the most common laboratory finding. In a group of patients (n = 101), a mean CSF protein concentration was 7 g/L (range: 1.5–10.3 g/L) [15]. High pressure is observed in 50 % of patients, while higher lymphocyte count can be recorded in 50–80 % [8, 15, 29]. Lymphocytic pleocytosis of CSF is moderate and is rarely higher than 250 cells/μL [8, 14, 15, 29]. A higher WBC count and the presence of neutrophils are uncommon; if present, they should warn about a possible infection [8, 42, 43].

In the retrospective analysis conducted by Shuster S. et al. (2017) in 31 patients (mean age: 45.6 years old), PCNSV was diagnosed only in 17 patients (55 %) using biopsy and in 14 patients (45 %) — with the help of high-resolution MRI. A group of investigators led by Shuster S. et al. (2017) found out that the CSF composition depends on the diameter of a damaged vessel. The following feature can be observed when analysing CSF: when small vessels are involved, cytosis (16 cells/μL) and protein (98 mg/dL) are present, while in case of medium-sized/large vessel involvement, these values tend to decrease four-fold (cytosis: 4 cells/μL, protein: 56 mg/dL) [8, 42].

These values show that the pathological process is highly active, and they need to be measured in order not to overlook similar diseases (infections: varicella-zoster virus, hepatitis C and B, syphilis, human immunodeficiency virus, TB; autoimmune: exanthematous lupus erythematosus, rheumatoid arthritis; malignancies), due to the lack of specific PCNSV markers [8, 14-15, 41-43].

Currently, biomarkers that make it possible to diagnose PCNSV in blood serum and CSF are being searched for. Special attention is paid to the role of immune mechanisms (T- and B-cell immunity, cytokine storm) in development of inflammation in the vessel wall. There is a limited number of studies dedicated to the role of dendritic cells (DC) in the adventitia and media of medium-sized and large arteries in various diseases and pathological conditions where the immune system is involved. Normally, the vessel wall is intact to the exposure by the immune system (it is not destroyed as a foreign tissue), but only with defective DC caused by pathological DC stimulation by Toll-like receptors. During this process, the vessel wall undergoes DC structure alternation, DCs grow in number, resulting in activation of T-cell inflow to the vessel wall via vasa-vasorum. Besides, a lot of effector cytokines can be found where a vessel is damaged (IL-6/IL-17 or IL-12/IFN-γ clusters), and they take part in steady inflammation sustention in the vessel wall [44-46].

However, a complex assessment of the impact of these immune mechanisms (T-cell immunity and cytokines) on the development of the inflammation in patients with PCNSV has not been performed. This new area (vascular immunology) is described just in single papers. T. Ruland et al. (2018) assessed T-lymphocite population in blood and CSF samples taken from 2 study groups.

Group 1 are the patients (n = 4) with PCNSV and large vessel involvement, where the diagnosis was made on the basis of clinical symptoms, cerebral angiography and MRI, and by ruling out a system inflammation. Controls were patients (n = 4) with idiopathic intracranial hypertension. Blood and CSF samples of patients with PCNSV demonstrated reduced CD3+ T-cell count vs. controls (p = 0.029). No other changes in T-cell population were found [47].

In the study by T. Ruland et al. (2018), A4-amyloid beta (APP) levels in CSF of patients with PCNSV were low. Proceeding from the results, the authors assume that its absence/low values in CSF of patients with PCNSV (451.44 ± 196.21 ng/mL) vs. controls (1513.7 ± 255.55 ng/mL); t = 5.61, p = 0.0000641, can be a marker of brain damage in PCNSV [47].

The study by Strunk D et al. (2018) evaluated the cell composition of CSF of 18 patients with PCNSV confirmed with brain biopsy (n = 4) and cerebral angiography (n = 14). It was found out that an increase in the lymphocyte count in CSF correlates with the brain biopsy results (lymphocytic infiltration) [48]. It is worth mentioning that the authors made the following assumption: immune cells in CSF can characterise the immune process in the CNS. In addition to the increase in the lymphocyte count in CSF, 33 % of patients had antibody-releasing cells, due to intrathecal Ig G synthesis. Therefore, this area needs further investigation, as the pathological role of T- and B-cell immunity and cytokines should be verified in larger cohorts [48].

A promising PCNSV marker in CSF is interleukin-17 (IL-17). IL-17 is a pro-inflammatory cytokine and a potent cell immunity mediator. Deb-Chatterji M (2019) et al. reported that the level of IL-17 produced by CD4+ T-cells in CSF was higher than normal in patients with PCNSV (sensitivity: 73 %, specificity: 100 %). Continuously increased IL-17 levels were observed in patients with active PCNSV and remission, evidencing that IL-17 is a more specific PCNSV biomarker that the number of cells and/or increased CSF protein and has crucial significance in the pathogenesis of this disease. These results tested in large cohorts will allow developing new therapeutic humanized anti-IL-17 antibody drugs for the management of PCNSV [49].

The circulating immune complex (CIC) is detected in blood with the help of immunomagnetic isolation or flow cytometry. Deb-Chatterji M (2019) et al. demonstrated that CIC values were increased significantly in patients with active PCNSV, but decreased with successful use of immunodepressants. Therefore, these results have a potential to facilitate diagnosis of cases with negative biopsy results and to monitor successful use of immunodepressants; however, further studies in larger number of patients are required [49].

Cerebral Angiography

Many clinicians use cerebral angiography as a tool of choice for diagnosing PCNSV due to a relatively low risk compared to brain biopsy. The main angiographic diagnostic criterion for vasculitides is multifocal, continuous or intermittent stenosis with areas of dilated vessels. This imaging pattern is not always specific, since it can be observed in other pathological processes: vessel wall spasm and/or edema, emboli in cerebral vessels; therefore, correct PCNSV diagnosis requires correlation with clinical and laboratory data [8, 13, 15-18, 21, 26]. It is worth mentioning that angiographic results show the typical signs of PCNSV more often in the damage to medium-sized/large vessels, compared to involvement of small vessels, because of low angiographic resolution [8, 13, 15, 16].

Raghavan A. et al. (2019) compared two methods (cerebral angiography and brain biopsy) in 128 patients (mean age: 49.8 years old) with PCNSV. It was found out that only 5 patients (21.74 %) out of 23 patients with confirmed biopsy results had typical angiographic presentation of PCNSV. Also, examination of 70 patients with negative biopsy results demonstrated that only 46 patients had typical angiographic changes [50].

Disadvantages of the practical use of this method include extreme invasiveness. This examination in not recommended in patients with renal disorders, because the contrast dye is toxic. Therefore, an improvement in this method with a better image quality and higher resolution will allow detecting inflammatory changes even in small arteries [1,8-9, 13, 15-17].

Brain Imaging

Patients with suspected PCNSV undergo a mandatory MRI assessment of the changes in their brain substance, cerebral blood flow assessment using magnetic resonance angiography (MRA) and computer angiography (CTA), contrast assessment of the vessel wall using high-resolution MRI (HR-MRI) [1, 8-9, 11, 13, 15-17, 28].

Changes in the brain substance detected by MRI are non-specific and are more common in the damage to medium-sized/large arteries. The bed of a damaged vessel shows single or multiple foci (hypointense in T1 and hyperintense/heterogeneously changes in T2 or FLAIR); where the contract medium is used, it accumulates suing a cerebrovascular accident. In turn, in small vessel vasculitides, various variants can be observed: multiple brain infarctions in both cerebral hemispheres, irregular areas of subcortical vasogenic edema (hyperintense in T2 or FLAIR, isointense in T1), parenchymatous hemorrhage (8 to 55 %) [8, 11, 15]. In the study by Schuster S. et al. (2017), brain substance examination

revealed atrophy in cortical and subcortical structures, caused by transmural inflammation of small arteries confirmed with biopsy. Contrast uptake by cerebral meninges is observed more commonly in small vessel vasculitides compared to the damage to large vessels (60–77 % vs. 22–29 %) [8, 42].

It is worth mentioning that pseudotumor PCNSV is a rare pathology (approximately 15 %) and its diagnosis is challenging. In contrast brain imaging, this condition resembles other pathologies, such as malignancies, pseudoneoplasms or brain abscesses [8, 12, 15].

According to Charidimou A. et al. (2017), 12 % of patients have tumour-like foci [51]. A distinctive brain imaging evidence of A-β-associated angitis which allows distinguishing cerebral amyloid angiopathy (CAA) is contrast uptake by meninx vasculosa with or without infiltrative changes (70 % vs. 7 %) and rare lobar hemorrhage (7 % vs. 62 %) [39]. In the study by Salvarani C. et al. (2015) 80 patients out of 149 patients with PCNSV had brain infarctions (in medium-size/large artery involvement — 66 %, in the damage to small arteries — 34 %) [21]. In another study by Schuster S. et al. (2017), brain MRI revealed a typical pattern of brain infarction in the damage to medium-size/large arteries (85.7 %) vs. small vessel involvement (29.4 %). Therefore, MRI is a highly sensitive method (95–100 %), but possesses low specificity, and the vessel bed needs a MRA assessment [42].

It is worth mentioning that MRA and CTA images show areas of even or mildly uneven stenosis intermitting with delated areas, in one or several arteries, vessel abnormalities (single or multiple stenoses and/or occlusions) [8, 11, 13, 15-17].

MRA allows for comprehensive assessment of the vessel wall, while CTA is better in identifying the rate of stenosis and blood flow and a bypass network. In turn, the practical application of MRA and CTA in small vessel involvement is impossible due to the lack of angiographic changes. Thus, these methods have low specificity compared to the traditional contrast cerebral angiography [8, 30, 42].

Previously described methods do not make it possible to distinguish between inflammatory and non-inflammatory vasculopathies. In order to differentiate PCNSV from other/non-inflammatory vasculopathies, the vessel wall is now examined with contrast enhancement in HR-MRI dark-blod-fat-sat mode (fat and blood psychic inhibition), allowing to improve imaging [8, 12-13, 15-18, 35]. The key differentiator in PCNSV is smooth, concentric and segmental thickening of the vessel wall with contrast uptake and perivascular edema [8, 15, 29, 42]. Noh H. et al. (2016) noted that contrast uptake allows diagnosing PCNSV at an early stage of the pathologic process, when cerebral angiography is inefficient [30]. Besides, this phenomenon allows differentiating from atherosclerotic vascular disease, since unlike PCNSV, an atherosclerosis plaque is eccentric, with local vessel wall thickening without any signs of perivascular edema, and the contrast uptake depends on its composition (from moderate to high intensity) [8, 12-13, 15-18, 35, 42]. This method will be developed further and its resolution will improve in the clinical practice, thus making in possible to diagnose inflammation of small arteries.

Brain Biopsy

Currently, the golden diagnostic method for PCNSV is still brain biopsy, however, it successfully diagnoses histopathological abnormalities only in 50–75 % of cases [13]. Since cerebral angiography is inefficient in the damage to small arteries (the results are negative), brain biopsy is one of the most useful verification methods [14, 15, 25].

Very often cerebral vessel biopsy yields little information, in 50 % of cases it is false-negative, if a sample is taken from an unaffected area in case of focal and/or segmental involvement. Therefore, a single negative biopsy result does not rule out PCNSV. In order to reduce the false-negative results rate, the following additional methods are used: MRI to search for an abnormality in an expected damage area; leptomeningeal test (the diagnostic level increases to 87 %). In a majority of cases, biopsy is performed for differentiation from widespread vasculitis (either autoimmune or infectious), non-inflammatory vasculopathies (reversible cerebral vasoconstriction syndrome) or malignancies (lymphoproliferative disorders) [8, 23, 29].

Morphologically, PCNSV is divided into three most common histopathology variants: granulomatous vasculitides, lymphocytic vasculitides, necrotising vasculitides (Figure 2). Mixed variants are observed as well. Histological patterns remain stable over time, therefore, it can be assumed that these patterns do not correspond to various disease stages [12-13, 15-18, 24].

Morphological changes in PCNSV are noted in medium-sized arteries and arterioles. Damage to veins is uncommon (the endothelium remains intact); there are rare cases of isolated medium-size alba vein involvement [51]. The study by Mlakar J et al. (2016) describes for the first time a case report of PCNSV with granulomatous vein inflammation (phlebitis) in a 22-year-old woman manifesting with acute headache. Biopsy sample morphology demonstrated vasculocentric mononuclear infiltration associated with well-defined granulomas and/or multinucleated giant cells through the vessel wall [8, 52].

β-A4 amyloid deposits are common in granulomatous vasculitides, but are not unique for this type,

therefore, biopsy is required for differentiation from cerebral amyloid angiopathy (CAA). A distinctive histological feature making it possible to differentiate between CAA and PCNSV is perivascular inflammatory response (infiltration with mono- and polynuclear cells), where granulomas are not typical [8, 39-41, 52].

The incidence of lymphocytic vasculitides comes second among histopathological variants of PCNSV; its manifestations include marked lymphocytic inflammation with sparse plasma cells, usually in several layers. Necrosing vasculitides is the rarest variant; its manifestations include transmural fibrinoid necrosis, that resembles nodular polyarteritis. The development and progression of necrosing vasculitides result in intracerebral bleedings and microaneurysms (12 %). In PCNSV, brain biopsy samples demonstrate ischemia in 40–51 % of cases [8, 12, 13, 16, 18].

The paper by C. Salvarani et al. (2015) includes the results of a retrospective analysis of 163 patients with PCNSV who underwent assessment in Mayo Clinic in 1983 to 2011. Upon admission, patients presented with various neurological symptoms (headache, cognitive disorders, etc.). PCNSV was diagnosed if brain or spinal biopsy samples demonstrated transmural destructive inflammatory infiltrate in the artery wall, if there were segmental narrowing of the smooth artery wall, cerebral artery dilatation or occlusion in the absence of any changes in artery wall typical of atherosclerotic vascular disease.

A follow-up examination allowed excluding patients with the signs of system disorders (exanthematous lupus erythematosus and other) and infection. The patients did not have a history of exposure to vasoactive substances, migraneous or thunderclap headaches. The endpoint of the clinical study was death of the patient or last hospitalisation (mean follow-up: 12 months, range: 0–13.7 years). During the 12-month follow-up, 81 patients out of 163 patients with PCNSV had their brain or spinal cord biopsy taken. Following biopsy, PCNSV was diagnosed only in 58 patients (72 %). Biopsy sample analysis demonstrated the following histopathological variants: granulomatous vasculitides in 34 patients (59 %) (deposition of beta amyloid in vessel wall in 20 patients (34 %)); lymphocytic vasculitides — in 13 patients (22 %); necrotising vasculitides — in 10 patients (17 %); a mix of granulomatous and necrotising vasculitides was observed in 1 patient [15].

In turn, 105 patients had their PCNSV diagnosed with the help of cerebral angiography, including 82 patients who initially did not undergo biopsy. 23 patients who did not have any signs of vasculitides in their biopsy material presented with vasculitides in angiography [15].

Despite the fact that brain and meninx biopsy is the golden standard for diagnosing PCNSV and that it possesses high specificity, its sensitivity is not sufficient enough and makes 53–63 % and 50–70 % according to various sources [8, 13, 14].

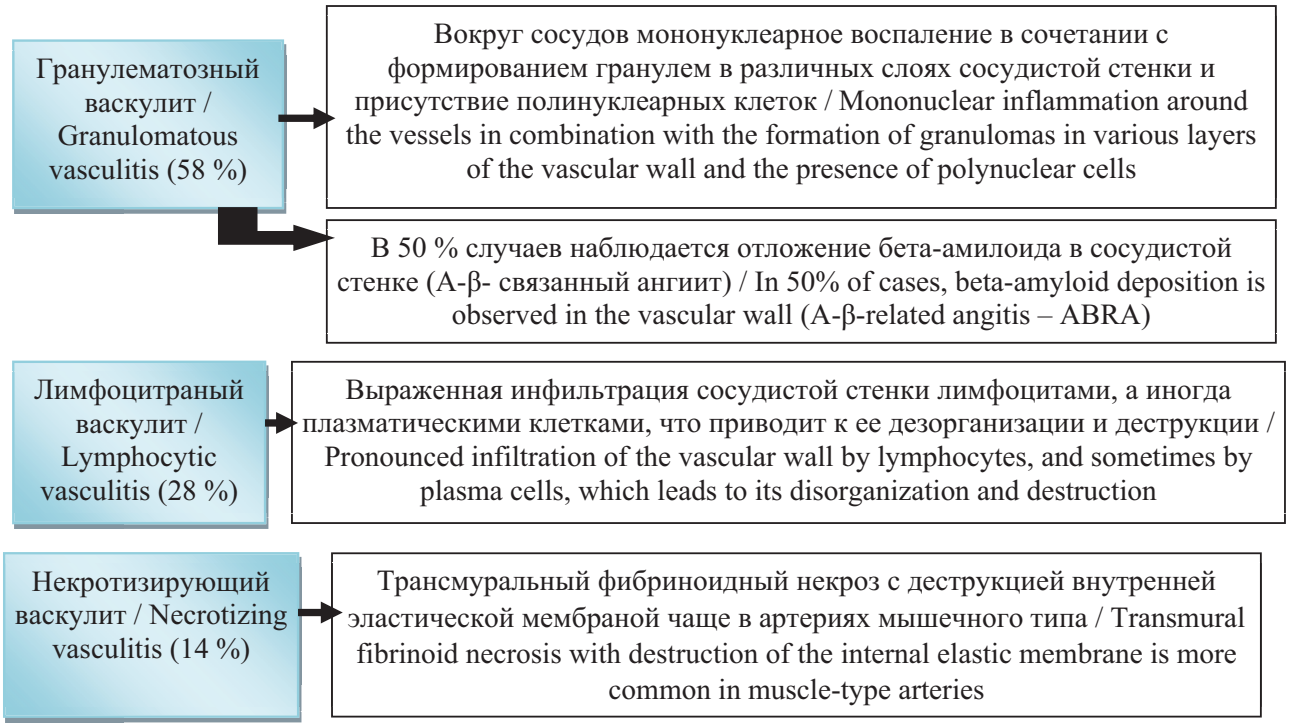

Figure 2. *Histopathological variants of PVCNS*

Conclusion

Despite the new knowledge of clinical presentation and diagnostic methods of PCNSV, this form of vasculitides remains understudied. Early identification of such non-specific common clinical presentations of PCNSV as headache, cognitive dysfunction and long-lasting neurological disorders (transient ischemic attack, aphasia, seizures, ataxia, sharp hemiparesis, semi-sensory loss, loss of fine motor skills, hemifacial weakness, etc.), will help in timely identification of patients with suspected disease, referral to clinical and laboratory tests, instrumental examinations, including brain biopsy. Untimely diagnosis of PCNSV will result in patient disability and/or death within a year. A major part of patients with PCNSV cannot work or experience challenges in professional life. PCNSV development and progression cause cognitive disorders, depression, anxiety, resulting in the reduction of quality of life of patients and their families. Taking into account the lack of specific blood and CSF markers, and also non-specific nature of cerebral angiography; limitations in the use of brain imaging methods (changes in brain substance during MRI, assessment of the cerebral blood flow during magnetic resonance angiography (MRA) and computed angiography (CTA), contrast high-resolution MRI (HR-MRI) of the vessel wall); challenges with the use of brain biopsy as a routine method due to its highly invasive nature.

Despite these limitations, a clinical diagnosis needs to be made in every individual case, even if it is a suspected or controversial diagnosis, and laboratory and instrumental assessments need to be performed in order to rule out/confirm PCNSV.

Currently, some ongoing clinical trials investigate triggers and pathogenetic mechanisms of a pathological process in the vessel wall in PCNSV. It may happen that in future specific and sensitive biomarkers of vessel wall damage will be found and will be used for the development of new diagnostic algorithms or to improve the verified diagnostic criteria of PCNSV.

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