

# Progressive multifocal leukoencephalopathy – epidemiology, immune response, clinical differences, treatment

**Snopková S.<sup>1</sup>, Štourač P.<sup>2</sup>, Fašanecková L.<sup>1</sup>, Mihalčín M.<sup>1</sup>, Havlíčková K.<sup>1</sup>, Svačinka R.<sup>1</sup>, Volfová P.<sup>3</sup>, Snopek P.<sup>4</sup>, Husa P.<sup>1</sup>**

<sup>1</sup>Klinika infekčních chorob FN Brno a LF MU, Brno

<sup>2</sup>Neurologická klinika FN Brno a LF MU, Brno

<sup>3</sup>Interní hematologická klinika FN Brno a LF MU, Brno

<sup>4</sup>Fakulta humanitních studií UTB, Zlín

## ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a severe disease of the central nervous system with very high mortality. It is caused by the JC virus with high seroprevalence, at up to 80%. Development of PML is typically opportunistic, particularly in acquired immunodeficiency syndrome, and usually affects patients with profound immunodeficiency. Furthermore, as a result of highly efficient immunosuppressive and immunomodulatory treatments in recent years, the number of PML cases has increased

in the general population. In this article, the authors mention virological and epidemiological relationships and characteristic manifestations of PML. Possible relationships of humoral and cellular immunity are discussed and limited treatment options including prophylaxis are mentioned.

## KLÍČOVÁ SLOVA

**cellular immunity – CD4/CD8 ratio – HIV – multiple sclerosis – progressive multifocal leukoencephalopathy**

## SOUHRN

**Snopková S., Štourač P., Fašanecková L., Mihalčín M., Havlíčková K., Svačinka R., Volfová P., Snopek P., Husa P.: Progressivní multifokální leukoencefalopatie – epidemiologie, imunitní odpověď, klinické rozdíly, léčba**

Progressivní multifokální leukoencefalopatie (PML) je závažné onemocnění centrální nervové soustavy s velmi vysokou mortalitou. Příčinou onemocnění je JC virus s vysokou séroprevalencí dosahující až 80 %. PML je typické oportunní onemocnění vyskytující se zejména u syndromu získané imunodeficience u pacientů s hlubokým imunodeficitem. Počet případů PML se

však v posledních letech zvyšuje také u všeobecné populace jako důsledek vysoce účinných imunosupresivních a imunomodulačních léčebných postupů. V tomto článku autoři uvádějí virologické a epidemiologické souvislosti a charakteristické projevy PML. Jsou diskutovány možné vztahy humorální a buněčné imunity a jsou zmíněny omezené možnosti léčby včetně profylaxe.

## KLÍČOVÁ SLOVA

**buněčná imunita – poměr CD4/CD8 – HIV – sclerosis multiplex – progressivní multifokální leukoencefalopatie**

*Epidemiol. Mikrobiol. Imunol., 68, 2019, č. 1, s. 24–31*

## INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) with rapid progression and fatal outcome, which affects the white matter of the cerebral hemisphere [1–3]. It is caused by the JC virus (JCV), a polyoma virus found worldwide with high seroprevalence, at up to 80% [1, 4]. JCV was named after the patient with PML whose initials were J.C. in 1971 [4]. But PML is not the only a brain disorder. Besides the infection of **oligodendrocytes** also disorders induced by infection of neurons were detected. Other disorders that have been described include granule cell neuronopathy (GCN) of the cerebellum [5] and a fulminant JCV encephalopathy involving cortical pyramidal neurons [6, 7]. In addition, PML can present clinically as a JCV-associated meningitis in the absence of encephalitis [4].

The overall incidence of PML in the general population is recorded to be 4.4/100 000 inhabitants/year [8].

A dramatic 50-fold increase in the incidence occurred with the **human immunodeficiency virus (HIV) epidemic** [9]. Patients with HIV-1 infection make up 4/5 of all patients analyzed in literature [8]. PML is the 3rd most common infectious neurological disease seen in HIV-positive patients, and was an extremely rare disorder prior to the acquired immunodeficiency syndrome (AIDS) pandemic [10]. Development of PML is typically opportunistic and it usually affects patients with profound immunodeficiency due to HIV infection [1, 8]. The 1-year survival in HIV-positive patients treated with ART is 38–62% [11, 12]. Furthermore, as a result of highly efficient **immunosuppressive and immunomodulatory treatments** in HIV-negative patients in recent years, the number of PML cases has increased in this population [4]. In multiple sclerosis (MS), PML has been reported in two MS patients treated with fingolimod and in one patient treated with dimethyl fumarate [13]. PML was also reported in three patients receiving dimethyl fumarate both with and without lymphopenia, but these

patients were treated for psoriasis and not for MS [14]. Three cases of PML were reported in patients treated with natalizumab in 2004, two of them were treated for MS and one of them for Morbus Crohn. The drug was reintroduced in the market in 2006 with new precautions as monotherapy for relapsing-remitting MS patients with high disease activity. Despite this new precautions, additional three cases were diagnosed in 2008, nine cases were diagnosed in 2009 [15] and numbers of PML cases steadily rose with 566 confirmed cases by 2015 [16–19]. The global overall risk for patients on natalizumab is estimated to be 3.96/1000 patients [11, 20]. The risk of PML increases with **longer treatment duration** with maximum risk of 6.11–8.3/1000 patients at 24 months. Previous treatment with immunosuppressant drugs increases risk reaching a maximum incidence of 13/100 000 JC antibody negative patients on natalizumab for more than 49 months. The mortality rate in natalizumab associated PML is approximately 22%.

PML was originally rarely associated with lymphoma [21]. PML is also associated with other conditions such as other hematological malignancies, organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e. g. lupus, rheumatoid arthritis), and congenital immune deficiencies (e. g. idiopathic CD4+ T lymphocytopenia) [21, 22]. These populations account for less than 10% of all reported PML cases [23].

Taken together, conditions associated with PML are as follows: HIV-AIDS defining 1/100/year without ART; 6/10 000/year with ART; hematologic malignancies 8.3/100 000/year in lymphoma; rheumatologic conditions 1/100 000/year, organ transplants (heart, lung, kidney) 1/1000; bone marrow transplants 3.5/10 000/year; immunomodulatory treatments (i. e. in MS) 1/1000/year [11, 20].

## THE JCV GENOME

JCV is a dsDNA naked neurotropic polyomavirus; but it is still incompletely understood how the virus infects the CNS [9]. Severe, prolonged immunosuppression may lead to JCV dissemination to the CNS from sites of persistence (kidney, bone marrow, lymphoid organs, tonsils, spleen), or to reactivation of dormant virus already present in the CNS [24, 25].

Nucleotide sequence analysis of JCV in peripheral blood mononuclear cells (PBML), urine, and cerebral spinal fluid (CSF) of PML patients has revealed JCV sequence variations and rearrangements that influence viral pathogenicity and tropism [24, 26, 27].

JCV persists in at least two forms: a **non-pathogenic form (archetypal virus)** and a neurotropic form that contains a rearranged non-coding control region (NCCR) [23, 24, 28].

Kidney-resident archetypal JCV strains which was isolated from the urine of healthy individuals, is highly conserved [7]. The archetypal virus was isolated from sewage samples from different geographical areas suggesting a possible transmission by contaminated food, water and fomites [29].

Archetypal JCV strains can turn into **neurotropic JCV strains during immunosuppression** [7, 9, 30]. Upon immunosuppression and reactivation of the virus, rear-

rangements within the hyper-variable region occur and contain determinants for neurotropism and neurovirulence correlating with viral spread and development of PML [7, 31].

Glial cells (the main targets of JCV in the brain) and B cells, but not T cells, both express nuclear **DNA binding proteins** that interact with the regulatory region of the JCV genome and may permit JCV replication [24]. Two **transcription factors (NF-1 $\kappa$  and Spi-B)** important for JCV genome transcription are upregulated in glial cells, B cells and hematopoietic progenitor cells [24, 27, 32]. Spi-B binding sites are present in the promoter/enhancer of JCV neurotropic variants but not in the archetypal virus [24]. Replication of the JCV genome is dependent on a viral protein, termed **T antigen (T-ag)**. T-ag contains several functional regions, including **the helicase domain** [7.33–35]. T-ag is a hexameric protein with a helicase activity that is powered by ATP binding and hydrolysis. The helicase and ATPase function is critical for viral replication [35]. The induction of early gene transcription by JCV T-ag is the first step in viral replication and a key potential target for blocking reactivation of JCV [33, 36, 37].

Thus, the following conditions are required for JCV-induced PML to occur: changes in the NCCR that enhance viral transcription and replication; presence of transcription factors that bind to the rearranged NCCR; immunodeficiency [24]. Other factors such as an individual genetic predisposition may also be necessary [11, 24, 38].

## IMMUNOPATHOGENESIS OF PML

**Innate immunity** plays a central role in CNS protection against a variety of neurotropic viruses [39]. On the other hand, symptomatic JCV infection of the CNS is associated with disturbances of adaptive immunity affecting B cells, antibodies, and CD4+ and/or CD8+ T cells. But it is still not fully understood, **which components of the immune system prevents development of PML and which immune mechanisms are involved in eliminating the virus from CNS** [30]. Upon the suppression of CD4+ and CD8+ T-cell mobilization, as occurs with HIV infection or during immunomodulating therapy, the JCV enters the brain, either with B cells or as a cell-free virus, where it infects and kills oligodendrocytes, leading to demyelination [9]. Patients who develop PML have **a pathogenic form of the virus**, with specific changes in the regulatory region and the major viral capsid protein VP1 that may facilitate the spread of the virus from the periphery to the brain [40].

**B cells**, the antibody producing cells of the immune system, can serve as a viral reservoir and may help disseminate the virus in the brain [20, 24]. At the same time B cells are not an important component of the adaptive immune response which do not may play a role in JCV control [24]. Neutralizing antibodies against JCV, typically found in most individuals, neither protect against the development of PML, nor effectively clear the virus from the body [36]. Intrathecal synthesis of oligoclonal antibodies against VP1, the major structural protein of JCV, is also found in PML patients, but its protective effect is unclear [24] and the **humoral response alone is inefficient at clearing JCV infected cells** [15].

## SOUHRNNÉ SDĚLENÍ

Many disorders lead to oligoclonal IgG bands (OBs) in serum, which may also be presented in the CSF due to disruption of the blood-brain barrier (BBB). Identical OBs in CSF and serum (type 4) – so called “mirror-pattern” – suggest systemic immune activation, without local IgG synthesis in the CNS. OBs in the CSF with additional identical OBs in both CSF and serum indicate systemic and intrathecal immune activation (type 3) – a combination of type 2 and 4. Presence of OBs type 2 confirmed intrathecal IgG production without systemic activation suggests an alteration in the CNS parenchyma or CSF compartment. It is non-specific and can be demonstrated in numerous affections of the CNS [41]. In fact it is unclear what the OBs are [42].

The role of B cells in JCV infection and PML is likely more complex. B cells may help to control JCV infection through functions other than antibody production. B cells secreting Th1-type cytokines such as INF- $\gamma$  probably enhance the Th1 response and thereby help to establish effective CD8 T cell activity against JCV [24].

**Cell-mediated immunity** plays a more effective role in clearing initial or reactivated JCV infection before PML occurs [43]. Cellular immunity and increase in **CD4+ cell counts** appears to play a crucial role in the control of the JCV infection [24]. Several lines of circumstantial evidence exist suggesting that CD4+ helper T cells are crucial to the prevention of JCV spread [36]. Specific CD4+ T cells have been detected in the blood of patients who have survived PML, and the number of these cells correlates with JCV clearance from the CSF [9]. However, **CD4+ T cell count alone cannot predict disease progression**, suggesting that other cell types are also crucial for viral containment [36, 44].

**A low CD4/CD8 ratio** reflects immunologic dysregulation because cytotoxic CD8+ cells (CTLs) are extremely destructive and induce apoptosis in the target cells [45]. Expansion of the CD8+ compartment is accompanied by adverse cellular changes and excessive defense anti-JCV response. This CD8+ CTL response plays an important role in controlling replication of JCV by killing infected cells [4] and controlling replication of many viruses [36].

CTLs recognize the epitopes of viral proteins presented on the class I HLA molecules preventing further spread of the virus. Increased CTLs are usually detected in the blood of PML survivors [9, 17], in PML lesions where they aggregate around infected cells and rarely in patients with PML, who have a fatal outcome within 1 year from disease onset [9]. Even if the CD8+ T cell population stayed constant, the CD4/CD8 ratio has improved with improvement in the CD4+ count alone. It also seems to lead to normalization of immunological functions. A reduction of the CD4/CD8 ratio might facilitate the occurrence of PML [46]. More recent studies have suggested that while overall CTL responses are dampened in PML patients, those patients who do elicit a CTL response against T-antigen or VP1 may have better clinical outcomes [47]. Comparatively, PML seen in MS patients on natalizumab appears to be associated with a better clinical outcome compared to the course of the disease in HIV-1 positive PML patients [18, 36]. It suggests that the **ability to effectively reconstitute relevant lymphocyte populations** within the CNS is a critical feature of survival [48]. HIV-positive patients have long-term T cell depletion and a limited regenerative potential.

### PML-IRIS

In the immunocompromised host, classical PML causes lytic infection of oligodendrocytes and morphological changes of astrocytes in the absence of an inflammatory response [49, 50].

Once immune function is restored following ART in **HIV-positive patients**, adaptive immune mechanisms lead to an inflammation in the area of the PML lesion, which is referred to as **immune reconstitution inflammatory syndrome (IRIS)**. Inflammation in IRIS also seems to be driven by a dominant cytotoxic T cell response, which is massively exaggerated during IRIS [4]. Although the immune mechanisms underlying IRIS mediate the elimination of JCV from the brain, the resulting inflammation can cause additional brain damage and may lead to the death of the patients.

Immune reconstitution in PML can lead to IRIS in 10 to 30% of HIV-positive patients [49].

Another risk population is patients treated with **natalizumab**, mainly anti-JCV positive patients. IRIS is caused by an **excessive immune response and inflammatory damage to neuronal and glial tissue**. In natalizumab cases after the effective clearing of natalizumab, lymphocytes enter the central nervous system to attack JCV. The clinical impact of IRIS should not be underestimated, because it can worsen the disability and increase mortality to up to 30% [18].

The risk increases significantly after 2–4 years of treatment. IRIS is observed in majority (70%) of patients within days or weeks following discontinuation and removal of natalizumab [23]. In some studies PML-IRIS is found in up to 86% [14]. The survival rate is 77%, however, 40% of survivors suffered of severe disability, disability of 47% was classified as moderate and 13% developed mild disability [23].

### CLINICAL SYMPTOMS

Common **clinical findings** include motoric weakness, gait abnormalities, mono- and hemiparesis, visual field deficits, speech and language disturbances, and incoordination. Symptoms tend to progress rapidly over several weeks to months [12, 51, 52, 53].

PML should be considered in the differential diagnosis of any MS patient on **natalizumab** treatment with new neurological symptoms. The PML must be considered in any MS case treated with natalizumab when new neurological symptoms emerge. If the diagnosis is delayed, symptoms progression may accelerate and worsen over time.

The clinical presentation of PML in natalizumab-associated cases is heterogeneous and may include focal and non-focal neurological deficits including neurobehavioral, motoric, language and visual functions. Cognitive deficits usually are not the most common symptoms. However, rare brainstem involvement causes the most severe symptoms. PML can also be detected in patients who are asymptomatic – then the first symptoms can be non-specific and subtle and may be considered as symptoms of a multiple sclerosis relapse [54, 55]. Symptoms in the mid and later stages of the disease can be diagnosed as stroke or seizures disorder; especially seizures occur in 20% of patients with PML [56]. In HIV-positive

patients the most common findings at the time of initial physical examination were weakness (54%), followed by gait abnormalities (20%), cognitive abnormalities (20%), dysarthria (24%), aphasia (19%), sensory loss (19%), visual impairment (17%), and oculomotor palsy (6%). In some cases, the coexistence of encephalitis with HIV infection could have accounted for some of the symptoms [53]. The mortality rate in natalizumab-associated PML cases is approximately 22% [57]. This is a considerably lower number than in the HIV-associated form with rapid progression and fatal outcome [18]. But the survivors suffer in 90% by moderate or severe disability.

## DIAGNOSIS OF PML

No single criterion establishes the diagnosis of PML. It requires clinical, imaging, and virological evidence. However, a working group of the **American Academy of Neurology (AAN)** has proposed an algorithm for the diagnosis of this disease. The presence of classic radiographic findings and clinical features consistent with diagnosis, coupled with a positive CSF JCV polymerase chain reaction (PCR) is sufficient for the unequivocal diagnosis of PML [51].

The first step in positive diagnosis is **magnetic resonance imaging (MRI)**. Cranial MRI is very sensitive to the presence of white matter lesions. Irregular multifocal lesions of demyelination occur usually in parietal, frontal or occipital lobes and less often in temporal lobes [12, 19, 51–55]. Currently there is no consensus how often **MRI scan** should be done in MS patients on natalizumab treatment, but usually MRI scans are performed every 3–4 months in the subgroup of patients with the highest risk of PML with the aim to catch the preclinical stage of PML and to ensure a better prognosis.

The presence of JCV antibodies in the serum of MS patients expressed and stratified as JCV **antibody index** reflects the risk in a semi-quantitative manner. A high index value indicates that the risk to develop PML is significantly elevated, although probably about 99% of patients with this index value will not develop PML [60]. The value of the JCV antibody index in the range of 0–0.9 is considered negative, in the range 0.9–1.5 as a mild risk factor and values higher than 1.5 represent relatively high risk values [11, 20]. It is unclear why natalizumab patients with higher JCV antibody titers would be a greater risk of developing PML [36]. JCV antibody index can only reflect statistical risk estimations that need to be combined with individual risk-assessment [61].

**PCR detection of JCV DNA** in CSF can be used to confirm the PML diagnosis and has been shown to have diagnostic sensitivity of 70–80% and specificity of virtually 100% [7]. The sensitivity with newer ultrasensitive techniques is as high as 95% [62]. CSF sampling is of greatest value in demonstrating JCV presence by PCR [51]. Lower CSF JCV DNA at the time of diagnosis is related to less disability prior to PML diagnosis. High viral load of JCV DNA > 10,000 copies/ml of CSF is associated with poor prognosis [48]. The absence of JCV DNA by CSF PCR does not exclude the PML diagnosis and it therefore should not be assumed that the CSF compartment provides an accurate representation of infections within the brain parenchyma [36].

Examination of CSF samples (cell counts, CSF proteins, glycorrhachia) has no predictive value in diagnosing PML [1, 51]. Also, the absence of JCV in urine does not rule out the possibility of developing PML [63].

## TREATMENT

Specific PML treatment is not yet available [1, 8, 52]. **Reconstituting the protective immunity or reversing the immunosuppression** is so far the best way to eliminate JCV infection from the CNS and to overcome PML.

The therapy for the PML-IRIS syndrome includes high dose of **corticosteroids** to limit this excessive inflammatory reaction [65]. But the use of corticosteroids to treat IRIS may limit JC viral clearance [66]. In some cases maraviroc (antiviral agent) can be used as a corticosteroid-saving agent in the treatment of IRIS. In three cases, maraviroc did not show any clear effect in modulating the clinical course of PML preventing IRIS. Moreover, once PML-IRIS emerged, the clinical stabilization was achieved only with the use of corticosteroids. Thus, the use of maraviroc should be regarded with extreme caution according to some authors [67]. On the other hand although some investigators have recommended corticosteroid therapy for PML-IRIS, no controlled trials have been conducted and caution has been advised [53]. In some PML populations, immune reconstitution cannot be achieved - patients with depressed bone marrow, organ recipients, in whom it could lead to graft rejection. Some PML patients may not develop IRIS at all because of persisting severe immunosuppression related to haematological malignancy, or treatment with rituximab or alemtuzumab [49]. PML is a lethal disease for these patients. The only effective treatment option for these PML patients would be a **direct anti-JCV therapy**, which is currently unavailable [23, 49].

Previous studies have also identified the **5HT2A serotonin receptor** as a receptor for the virus, but most evidence suggest that the initial steps of viral infection can occur in a broad range of cell types. Since JCV infection of glial cells involves serotonergic 5HT2A receptors, medications targeting these receptors have also been proposed as potential adjuncts [25, 67, 68]. 5HT2A receptors inhibitors are active in vitro against JCV [69]. The atypical antidepressant **mirtazapine** has been shown to inhibit viral entry into unaffected glial cells and to block infection of oligodendrocytes with JCV, preventing further demyelination [25]. Use of the mirtazapine has been associated with clinical improvement in some PML patients, with earlier treatment related to better outcomes [67, 70].

**Mefloquine** works through a different mechanism, inhibiting JCV replication in cells after viral entry [71]. Mefloquine is able to cross the blood-brain barrier (BBB) and reach a concentration sufficient to suppress JCV replication in the brain by binding to the T-ag [23, 25, 71]. T-ag and its helicase domain are critical for viral replication [21]. Mefloquine showed significant suppression of JCV DNA replication [23, 72].

Moreover, mefloquine is an inhibitor of the efflux protein P-glycoprotein (P-gp) and it is an ATP-binding cassette (ABC) transporter [73–75]. ATP-binding cassette transporter

## SOUHRNNÉ SDĚLENÍ

ters are known to function as barrier proteins to extrude toxins and xenobiotics from cells. P-gp is critical among these transporters [76].

The case of a man with PML treated with mirtazapine and mefloquine has recently been described. Under treatment, the rearrangement changed toward the archetypal sequence [31].

In another case clinical progression of PML stopped immediately after mefloquine treatment was described in a woman with sarcoidosis [77]. However, the results of all observations are not entirely unambiguous and mefloquine did not show evidence of *in vivo* antiviral activity against JCV in some studies [78, 79]. A clinical trial of mefloquine in patients with PML had to be prematurely terminated due to lack of efficacy [79].

Potential candidate for treatment or prophylaxis of PML can be broadly categorized into three groups: antiviral agents, immune response modulators, and immunization strategies [23]. More identified potential drug candidates can be investigated. So far significant limitations in the development of treatment include e.g. lack of good animal PML models, the toxicity profile of potential anti-JCV drugs, the lacking ability to cross the BBB, recruitment of study subjects and others [23, 36].

Clinical settings concerning PML in natalizumab patients are continuously evolving in the MS treatment algorithm [11, 20]. The treatment and subsequent clinical course in patients with natalizumab-associated PML are based on restoration of immune functions by immediate removal of drug [64]. This is typically done by **plasma exchange or immunoadsorption** which clears natalizumab from the circulation. Three to five plasma exchanges usually are required over two weeks. Discontinuation of monoclonal antibody treatment triggers rapid expansion and enhanced trafficking of immune cells across the BBB and often leads to the development of immune-mediated IRIS and the temporary worsening of clinical symptoms [36]. Some PML patients treated with plasma exchange will experience rapid worsening of neurological symptoms after clearance and develop IRIS [4]. MS patients, after temporarily stopping the immunomodulatory agent, have to begin a new with some other immunomodulatory agent to prevent progression of their MS disease. It means a relapse is possible.

**Antiretroviral therapy** should be started immediately in HIV-positive patients [1, 52]. Disease progression seems to be slower in patients on effective ART [1,8], because the most important determinant for survival is restoration of the immune system [53] and HIV-positive patients stay on lifelong ART.

### RECAPITULATION

In the classical era, PML was an extreme rare disorder which occurred in patients with lymphoproliferative and myeloproliferative disorders possibly due to a lack of a JCV specific immune response as a result of uncontrolled expansion of other immune cell types due to the cancer. PML became exponentially more prevalent with the onset of the HIV-1 pandemic. HIV-1 positive patients with depleted CD4+ T cell counts, became increas-

ingly vulnerable to the development of PML, suggesting that this cell type plays an important role in immune surveillance of JCV [36]. More recently, cases of PML have been documented in immunocompromised patients undergoing immunosuppressive and immunomodulatory therapy, which seems to disrupt normal immune surveillance by CD8+ T cells in the CNS and allows for the uncontrolled reactivation of JCV and the PML onset [9, 36]. Also PML has been reported in the number of distinct immunodeficiency such as Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome, X-linked hyper-IgM syndrome, hyper IgE syndrome, adenosine deaminase deficiency, X-linked agammaglobulinemia, purine nucleoside phosphorylase deficiency and others [38, 49]. Immunodeficiency is highly relevant risk factor, but alone does not predict who will develop PML, since the vast majority of individuals with classical risk factors will not develop the disorder. Other factors need to be considered and there is growing evidence for the role of **host genetic factors** in susceptibility to PML [38].

The biological properties, the pathological transformation and the life cycle of the JCV in the host organism are still poorly understood. Recent data suggest that CD4+ and CD8+ T cells of the cellular immune system are crucial to the prevention of JCV spread. Some research suggests that the occurrence of PML in the context of B-lymphocyte depletion are not the principal vehicle for JCV to enter the brain, but also that humoral immunity might play a role in the control of JCV replication [46]. So far, we know very little about the interaction of different virological, immunological, genetic and other factors that allow some individuals to clinically manifest PML.

There is no effective therapy for treating JCV infections and fatal PML [62]. Treatment is complicated. The main approach to treatment is **to preserve immune function or reverse immunosuppression**. The most important determinant for survival is restoration of the immune response by antiretroviral therapy in HIV-positive patients and discontinuation of immunomodulatory therapy in HIV-negative patients. But only a minority of these patients recover with mild to moderate disability [23], because these measures are not a factual PML treatment, but only **non-specific measures** that reduce the impact of immunodeficiency as a risk factor for development of PML.

However, it is not always possible to stop immune suppression, for example in organ transplant patients, in whom it could lead to graft rejection, in patients with persisting severe immunosuppression related to hematological malignancy or in patients with immunosuppression during chemotherapy of solid cancers [49]. Outcomes in these PML populations are poor [23]. There is no effective specific antiviral therapy for treating as well as preventing JCV infection or PML [62]. Completed and published PML treatment clinical studies reveal the difficulty of studying potential therapies, including rarity and rapid progression of the disease and short life expectancy.

Studies aimed at **prevention of PML** may have a better chance at delivering positive outcome [23]. Prevention of progressive immunosuppression by initiation of antire-

troviral therapy is the most effective way to prevent PML in HIV-positive patients [52]. **Active prophylactic immunization** of healthy individuals or patients under treatments with PML risk has the potential to prevent PML or, in seronegative individuals, even the establishment of latent/persistent infection altogether. The **active therapeutic immunization** would be most suitable for patients with residual and restorable immune function [49] whereas **passive immunization** would be an attractive alternative for populations in which immune system response cannot be boosted due to chronic immunodeficiency [23].

## CONCLUSIONS

With the introduction of antiretroviral treatment, the incidence of PML in HIV-positive patients decreased, but the growing use of immunosuppressive and immunomodulatory therapies for various diseases has led to an alarming increase of PML cases among patients with conditions that were previously not associated to any significant PML risk. We can expect to meet PML more frequently than hitherto due to the high seroprevalence of the JCV and a worldwide distribution in the population. A better understanding of the complex relations between JCV and different cell compartments may have significant implications for the prevention and treatment of PML. Accurate identification and stratification of the risky populations, as well as biomarkers and cytokine profiles which are evidence of JCV activation are needed to monitoring and early intervention. Also important is the development of specific drugs and prophylaxis. Further biological, clinical and pharmacological research and studies are necessary.

## REFERENCES

- Hoffmann C. Opportunistic infections. In: Hoffmann C, Rockstroh JK. HIV 2015/2016. Hamburg: Medizin Fokus Verlag; 2015. pp. 377–380.
- Smolle E, Trojan A, Schuster SJ, et al. Progressive multifocal leukoencephalopathy – a case report and review of the literature. *In Vivo*, 2014;28(5):941–948.
- Sudhakar P, Bachman DM, Mark AS, et al. Progressive multifocal leukoencephalopathy: recent advances and a neuro-ophthalmological review. *J Neuroophthalmol*, 2015;35(3):296–305.
- Bauer J, Gold R, Adams O, et al. Progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome (IRIS). *Acta Neuropathol*, 2015;130(6):751–764.
- Koralnik IJ, Wuthrich C, Dang X, et al. JC virus granule cell neuronopathy: a novel clinical syndrome distinct from progressive multifocal leukoencephalopathy. *Ann Neurol*, 2005;57(4):576–580.
- Wuthrich C, Dang X, Westmoreland S, et al. Fulminant JC virus encephalopathy with productive infection of cortical pyramidal neurons. *Ann Neurol*, 2009;65(6):742–748.
- Shin J, Phelan PJ, Chhum P, et al. Analysis of JC virus DNA replication using a quantitative and high-throughput assay. *Virology*, 2014;468–470:113–125.
- Rozsypal H, Jilich D, Hubacek P, et al. Úskalí diagnostiky progresivní multifokální leukoencefalopatie u pacientů infikovaných lidským virem imunodeficiency – kazuistiky. *Cesk Slov Neurol N*, 2013;76/109(4):501–507.
- Bellizzi A, Anzivino E, Rodio DM, et al. New insight on human polyomavirus JC and pathogenesis of progressive multifocal leukoencephalopathy. *Clin Dev Immunol*, 2013;2013:839719 [cit. 2017-12-12]. Dostupné na [www: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652120/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652120/)
- Delbue S, Elia F, Carloni C, et al. JC virus load in cerebrospinal fluid and transcriptional control region rearrangements may predict the clinical course of progressive multifocal leukoencephalopathy. *J Cell Physiol*, 2012;227(10):3511–3517.
- Mateen FJ, Muralidharan R, Carone M, et al. Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol*, 2011;70:305–322.
- Augusto L, Neves N, Reis C, et al. Clinical and radiological characterization of progressive multifocal leukoencephalopathy in HIV-infected patients: A retrospective analysis and review of the literature. *Acta Med Port*, 2015;28(3):286–296.
- US Food and Drug Administration (2014): Drug safety and availability – FDA Drug Safety Communication: FDA warns about rare case of brain infection PML with MS drug Tecfidera (dimethyl fumarate) [cit. 2017-04-10]. Dostupné na [www: http://www.fda.gov/Drugs/DrugSafety/ucm424625.htm](http://www.fda.gov/Drugs/DrugSafety/ucm424625.htm)
- Ermis U, Weis J, Schulz JB. PML in a patient treated with fumaric acid. *N Engl J Med*, 2013;368(17):1657–1658.
- Linda H, von Heijne A Major EO, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med*, 2009;361(11):1081–1087.
- Nieuwkamp DJ, Murk JL, Van Oosten BW, et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. *N Engl J Med*, 2015;372(15):1474–1476.
- Perkins MR, Ryschkewitsch C, Liebner JC, et al. Changes in JC virus-specific T cell responses during natalizumab treatment and in natalizumab-associated progressive multifocal leukoencephalopathy. *PLoS Pathog*, 2012;8(11):e1003014 [cit. 2017-11-12]. Dostupné na [www: https://doi.org/10.1371/journal.ppat.1003014](https://doi.org/10.1371/journal.ppat.1003014).
- Vermersch P, Kappos L, Gold R, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurol*, 2011;76(20):1697–1704.
- Yousry TA, Pelletier D, Cadavid D, et al. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol*, 2012;72(5):779–787.
- Amend KL, Turnbull B, Foskett N, et al. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurol*, 2010;75(15):1326–1332.
- Power C, Brown Gladen JG, Halliday W, et al. AIDS and non AIDS – related PML association with distinct p53 polymorphism. *Neurol*, 2000;54(3):743–746.
- Aotsuka Y, Uzawa A, Nishimura K, et al. Progressive multifocal leukoencephalopathy localized in the cerebellum and brainstem associated with idiopathic CD4+ T lymphocytopenia. *Intern Med*, 2016;55(12):1645–1647.
- Pavlovic D, Patera AC, Nyberg F, et al. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord*, 2015;8(6):255–273.
- Durali D, de Goer de Herve M-G, Gasnault J, et al. B cells and progressive multifocal leukoencephalopathy: search for the missing link. *Front Immunol*, 2015;6:241 [cit.2017-07-10]. Dostupné [www: https://doi.org/10.3389/fimmu.2015.00241](https://doi.org/10.3389/fimmu.2015.00241).
- Epperla N, Medina-Flores R, Mazza JJ, et al. Mirtazapine and mefloquine therapy for non-AIDS-related progressive multifocal leukoencephalopathy. *WMJ*, 2014;113(6):242–245.
- Tan CS, Dezube BJ, Bhargava P, et al. Detection of JC virus DNA and proteins in the bone marrow of HIV-positive and HIV-negative patients: implications for viral latency and neurotropic transformation. *J Infect Dis*, 2009;199(6):881–888.
- Marshall LJ, Ferenczy MW, Daley EL, et al. Lymphocyte gene expression and JC virus noncoding control region sequences are linked

## SOUHRNNÉ SDĚLENÍ

- with the risk of progressive multifocal leukoencephalopathy. *J Virol*, 2014;88(9):5177–5183.
28. Bellizzi A, Nardis C, Anzivino E, et al. Human polyomavirus JC reactivation and pathogenetic mechanisms of progressive multifocal leukoencephalopathy and cancer in the era of monoclonal antibody therapies. *J Neurovirol*, 2012;18(1):1–11.
29. White MK, Khalili K. Pathogenesis of progressive multifocal leukoencephalopathy-revisited. *J Infect Dis*, 2011; 203(5):578–586.
30. Jelcic I, Faigle W, et al. Immunology of progressive multifocal leukoencephalopathy. *J Neurovirol*, 2015;21(6):614–622.
31. Kurmann R, Weisstanner C, Kardas P, et al. Progressive multifocal leukoencephalopathy in common variable immunodeficiency: mitigated course under mirtazapine and mefloquine. *J Neurovirol*, 2015;21(6):694–701.
32. Marshall LJ, Dunham L, Major EO. Transcription factor Spi-B binds unique sequences present in the tandem repeat promote/enhancer of JC virus and supports viral activity. *J Gen Virol*, 2010;91(12):3042–3052.
33. Bonafoux D, Nanthakumar S, Bandarage UK, et al. Fragment-based discovery of dual JC virus and BK virus helicase inhibitors. *J Med Chem*, 2016; 59(15):7138–7151.
34. Randhawa P, Zeng G, Bueno M, et al. Inhibition of large T antigen ATPase activity as potential strategy to develop anti-polyomavirus JC drugs. *Antiviral Res*, 2014;0:113–119.
35. Seguin SP, Ireland AW, Gupta T, et al. A screen for modulators of large T antigen's ATPase activity uncovers novel inhibitors of Simian Virus 40 and BK virus replication. *Antiviral Res*, 2012;96(1):70–81.
36. Beltrami S, Gordon J. Immune surveillance and response to JC virus infection and PML. *J Neurovirol*, 2014;20(2):137–149.
37. Sariyer IK, Merabova N, Patel PK, et al. Bag3-induced autophagy is associated with degradation of JCV oncoprotein, T-Ag. *PLoS One*, 2023;7:e45000 [cit. 2017-09-12]. Dostupné na [www: https://doi.org/10.1371/journal.pone.0045000](https://doi.org/10.1371/journal.pone.0045000).
38. Hatchwell E. Is there a (host) genetic predisposition to progressive multifocal leukoencephalopathy? *Front Immunol*, 2015;6:216 [cit. 2017-10-12]. Dostupné na [www: https://www.frontiersin.org/articles/10.3389/fimmu.2015.00216/full](https://www.frontiersin.org/articles/10.3389/fimmu.2015.00216/full).
39. Mori I. Transfactory neuroinvasion by viruses threatens the human brain. *Acta virol*, 2015;59(4):338–349.
40. Warnke C, Ramanujam R, Plavina T, et al. Changes to anti-JCV antibody levels in a Swedish national MS cohort. *J Neurol Neurosurg Psychiatry*, 2013;84(11):1199–1205.
41. Trbojevic M. Detection of oligoclonal Ig bands: clinical significance and trends in methodological improvement. *eJIFCC*, 2004;15 [cit. 2017-08-11]. Dostupné na [www: http://www.ifcc.org/ejifcc/vol-15no3/150309200413.htm](http://www.ifcc.org/ejifcc/vol-15no3/150309200413.htm).
42. Khanna N, Wolbers M, Mueller NJ, et al. JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. *J Virol*, 2009;83(9):4404–4411.
43. Monaco MCG, Major EO. Immune system involvement in the pathogenesis of JC virus induced PML: what is learned from studies of patients with underlying diseases and therapies as risk factor. *Front Immunol*, 2015;6:159 [cit. 2017-08-11]. Dostupné na [www: http://doi.org/10.3389/fimmu.2015.00159](http://doi.org/10.3389/fimmu.2015.00159).
44. Du Pasquier RA, Clark KW, Smith PS, et al. JCV-specific cellular immune response correlates with a favorable clinical outcome in HIV-infected individuals with progressive multifocal leukoencephalopathy. *J Neurovirol*, 2001;7(4):318–322.
45. Seng R, Goujard C, Krastinova E, et al. Influence of lifelong cumulative HIV viremia on long-term recovery of CD4+ count and CD4+/CD8+ ratio among patients on combination antiretroviral therapy. *AIDS*, 2015;29(5):595–607.
46. Sokol J, Lisá L, Zeleňáková J, et al. Rituximab – associated progressive multifocal leukoencephalopathy. *Vnitř Lék*, 2017;63(1):60–64.
47. Lima MA, Berna-Cano F, Clifford DB, et al. Clinical outcome of long/term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*, 2010;81(11):1288–1291.
48. Černý R, Machala L. Neurologické komplikace HIV/AIDS. Praha: Karolinum; 2007.
49. Jelcic I, Combaluzier B, Jelcic I, et al. Prevention and therapy of JC polyomavirus-mediated progressive multifocal leukoencephalopathy – a realistic possibility? *Swiss Med Wkly*, 2017;147:w14520 [cit. 2017-05-09]. Dostupné na [www: http://www.zora.uzh.ch/id/eprint/142365/1/Jelcic\\_et\\_al.pdf](http://www.zora.uzh.ch/id/eprint/142365/1/Jelcic_et_al.pdf).
50. Aly L, Yousef S, Schippling S, et al. Central role of JC virus-specific CD4+ lymphocytes in progressive multi-focal leukoencephalopathy-immune reconstitution inflammatory syndrome. *Brain*, 2011;134:2687–2702.
51. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria – consensus statement from the AAN Neuroinfectious Disease Section. *Neurol*, 2013;80(15):1430–1438.
52. Polsky B, Suh JS. Viral Infections. In Kuritzke DR, Eron JJ, Squires KE. *InPractice HIV* [on line]. Jointly Provided by USF Health and Clinical Care Opinions, LLC. 2014 [cit. 2017-11-09]. Dostupné na [www: http://www.inpractice.com/Textbooks/HIV/Management\\_of\\_Specific\\_Disease\\_States/ch29\\_pt1\\_Viral/Chapter-Pages/Page-5.aspx](http://www.inpractice.com/Textbooks/HIV/Management_of_Specific_Disease_States/ch29_pt1_Viral/Chapter-Pages/Page-5.aspx).
53. Berger JR. The clinical features of PML. *Cleve Clin J Med*, 2011;78(S2):8–12.
54. Boster A, Hreha S, Berger JR, et al. Progressive multifocal leukoencephalopathy and relapsing – remitting multiple sclerosis; a comparative study. *Arch Neurol*, 2009;66(5):593–599.
55. Coyle P, Foley J, Fox E, et al. Best practice recommendations for the selection and management of patients with multiple sclerosis receiving natalizumab therapy. *Mult Scler*, 2009;15:26–36 [cit. 2017-10-10].
56. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurol*, 2006;66(2):262–264.
57. O' Connor PW. Natalizumab risk stratification: role of two – step anti JCV antibody assay. *Can J Neurol Sci*, 2012;39(5):670–675.
58. Anzai Y. Infectious and demyelinating disease. Progressive multifocal leukoencephalopathy. In: Osborn AG, Salzman KL, Barkovich AJ. *Diagnostic imaging brain*. 2nd ed. Amirsys: Altona. 2010. p. 92–93.
59. Metz I, Radue EW, Oterino A, et al. Pathology of immune reconstitution inflammatory syndrome in multiple sclerosis with natalizumab-associated progressive multifocal leukoencephalopathy. *Acta Neuropathol*, 2012;123(2):235–245.
60. Reuwer AQ, Heron M, van der Dussen D, et al. The clinical utility of JC virus antibody index measurements in the context of progressive multifocal leukoencephalopathy. *Acta Neurol Scand*, 2017; 136(S 201):37–44.
61. Salmen A, von Ahsen N, Trampe AK, et al. Longitudinal analyses of anti-JCV antibody index for risk assessment of progressive multifocal leukoencephalopathy. *Mult Scler J Exp Transl Clin*, 2016;2:2055217316630008 [cit. 2017-10-10]. Dostupné na [www: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5433507/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5433507/).
62. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. October 28, 2014 [on line]. Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV medicine Association of the Infectious Diseases Society of America [cit. 2017-06-02]. Dostupné na [www: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/](https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/).
63. Polák P. Editoria on Sokol J, Lisá L, Zeleňáková J, et al. Rituximab – associated progressive multifocal leukoencephalopathy. *Vnitř Lék*, 2017;63(1):22–23.
64. Tan IL, McArthur JC, Clifford DB, et al. Immune reconstitution

- inflammatory syndrome in natalizumab-associated PML. *Neurology*, 2011;77(11):1061-1067.
65. Antoniol C, Jilek S, Schluep M, et al. Impairment of JCV-specific T-cell response by corticotherapy: effect on PML-IRIS management? *Neurology*, 2012;79(23):2258-2264.
66. Scarpazza C, Prosperini L, Mancinelli CR, et al. Is maraviroc useful in multiple sclerosis patients with natalizumab-related progressive multifocal leukoencephalopathy? *J Neurol Sci*, 2017; 378:233-237.
67. Himedan M, Camelo-Piragua S, Mills EA, et al. Pathologic findings of chronic PML-IRIS in a patient with prolonged PML survival following natalizumab treatment. *J Investig Med High Impact Case Rep*, 2017;5:2324709617734248 [cit. 2017-09-08]. Dostupné na [www: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5624358/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5624358/).
68. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*, 2004;306(5700):1380-1383.
69. Trentalange A, Calcagno A, Ghisetti V, et al. Clearance of cerebrospinal fluid JCV DNA with mirtazapine in a patient with progressive multifocal leukoencephalopathy and sarcoidosis. *Antivir Ther*, 2016;21(7):633-635.
70. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*, 2009;66(2):255-258.
71. Brickelmaier M, Lugovskoy A, Kartikeyan R, et al. Identification and characterization of mefloquine efficacy against JC virus *in vitro*. *Antimicrob Agents Chemother*, 2009;53(5):1840-1849.
72. Nukuzuma S, Kameoka M, Sugiura S, et al. Suppressive effect of PARP-1 inhibitor on JC virus replication *in vitro*. *J Med Virol*, 2013;85(1):132-137.
73. Kock K, Grube M, Jedlitschky G, et al. Expression of adenosine triphosphate-binding cassette (ABC) drug transporters in peripheral blood cells. *Clin Pharmacokinet*, 2007;46(6):449-470.
74. Barraud de Lagerie S, Comets E, Gautrand C, et al. Cerebral uptake of mefloquine enantiomers with and without the P-gp inhibitor elacridar (GF1210918) in mice. *Br J Pharmacol*, 2004;141(7):1214-1222.
75. Senarathna SM, Page-Sharp M, Crowe A. The interactions of P-glycoproteins with antimalarial drugs, including substrate affinity, inhibition and regulation. *PloS One*, 2016;11(4): e0152677 [cit. 2017-10-10]. Dostupné na [www: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821601/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821601/).
76. Oga EF, Sekine S, Shitara Y, et al. Potential P-glycoprotein-mediated drug-drug interactions of antimalarial agents in caco-2 cells. *Am J Trop Med Hyg*, 2012;87(1):64-69.
77. Gofton TE, Al-Khotani A, O'Farrell B, et al. Mefloquine in the treatment of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*, 2011;82(4):452-455.
78. Moenster RP, Jett RA. Mirtazapine and mefloquine therapy for progressive multifocal leukoencephalopathy in a patient infected with human immunodeficiency virus. *Am J Health Syst Pharm*, 2012;69(6):496-498.
79. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J Neurovirol*, 2013;19(4):351-358.
80. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology*, 2009;72(5):402-409.

**Do redakce došlo dne 19. 3. 2018.**

*Adresa pro korespondenci:*

**MUDr. Svatava Snopková, Ph.D.**

KICH FN Brno a LF MU

Jihlavská 340/20

625 00 Brno-Bohunice

e-mail: [Snopkova.svatava@fnbrno.cz](mailto:Snopkova.svatava@fnbrno.cz)