ESETISMERTETÉS
CASE REPORT

# Progressive multifocal leukoencephalopathy with a benign prognosis in an immunocompetent patient – A case report

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PRINT | English | https://doi.org/10.18071/isz.77.0060 | www.elitmed.hu

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**Érkezett:**
2022. október 7.
**Elfogadva:**
2023. május 24.

John Cunningham virus (JCV) is most commonly acquired in childhood and is often asymptomatic throughout life. However, in the case of primary or secondary immunosuppression, it is known to cause progressive multifocal leukoencephalopathy (PML) in the central nervous system. Hereby, we describe a rare case of PML in a patient without known factors of immunosuppression or use of immunomodulation. A 53-year-old female patient was presented with progressive left-side weakness and tremors in the left hand over a period of two months. The patient was diagnosed with PML based on history, examination, cerebrospinal fluid markers, histopathology, and brain magnetic resonance imaging at presentation. Despite detailed examination, nothing was found in the patient to cause an immunosuppressed state. Therapy was started with mirtazapine with significant neurological improvement.To our knowledge, PML in immunocompetent patient with bening prognosis is a very rare condition. There is also no effective treatment. Our case is a complicated example of this condition.

**Keywords:** John Cunningham virus, progressive multifocal leukoencephalopathy, mirtazapine

**Progresszív multifokális leukoencephalopathia jóindulatú prognózissal egy immunkompetens betegnél – esetismertetés**

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A John Cunningham-vírus (JCV) leginkább gyermekkorúakat fertőz, majd gyakran egész életben tünetmentes marad. Elsődleges vagy másodlagos immunszuppresszió esetén azonban ismert, hogy progresszív multifokális leukoencephalopathiát (PML) okoz a központi idegrendszerben. Ismertetjük a PML ritka esetét egy olyan betegnél, akinél nem ismert immunszuppressziót okozó tényező vagy immunmoduláció alkalmazása. Az 53 éves nőbeteg két hónapja tartó progresszív bal oldali gyengeséggel és a bal kéz remegésével jelentkezett. A betegnél jelentkezése után a kórelőzmény, a fizikális vizsgálat, a liquormarkerek, a szövettani vizsgálat és az agyi mágneses rezonanciás képalkotás alapján PML-t diagnosztizáltunk. A részletes vizsgálat ellenére a betegnél nem találtunk semmi olyat, ami immunszupprimált állapotot okozhatott volna. Mirtazapinterápiát kezdtünk, ami jelentős neurológiai javulást eredményezett. Ismereteink szerint a PML immunkompetens betegben benignus prognózissal nagyon ritka állapot. Nincs is hatékony kezelés. Esetünk ennek az állapotnak egy bonyolult példája.

**Kulcsszavak:** John Cunningham-vírus, multifokális leukoencephalopathia, mirtazapin

Progressive multifocal leukoencephalopathy (PML) is a fatal and demyelinating disease of the central nervous system that predominantly targets oligodendrocytes, caused by the John Cunningham virus (JCV), a DNA virus of the polyomviridae family that typically affects immunocompromised individuals. JCV commonly causes asymptomatic lifelong persistent or latent infection in the population[1].

Although about 50-90% of the adult population have antibodies to JCV, PML's incidence is estimated at about 4.5 per 100,000 people[2]. PML is characterized by a subacute onset, multifocal involvement of subcortical white matter, cerebellar hemispheres, and peduncles on a magnetic resonance imaging (MRI) scan. The clinical progress is subacute and the prognosis is generally poor, with a three-month mortality rate of 20-50% in untreated patients[3]. PML is classified as either HIV-associated or non-HIV-related, where the latter is caused by various conditions such as malignancy, chemotherapy, and immunosuppressants used for autoimmune diseases[4]. An increased prevalence of non-HIV-related PML has been observed with the use of monoclonal antibodies in the treatment of multiple sclerosis and/or haematological diseases[4]. Its differential diagnosis includes several diseases such as glioma, malignant lymphoma, multiple sclerosis and neuropsychiatric lupus, as well as infectious encephalitis because of various clinical presentations and MRI findings[3]. Diagnosis is based on clinical or radiological suspicion of the disease and by the detection of JCV DNA in the cerebrospinal fluid (CSF) using a PCR test. A definite diagnosis of PML can be made following a brain biopsy[5]. Antiretroviral therapy should be initiated in HIV-associated patients, current immunosuppressive therapy should be discontinued in non-HIV-related patients, and the agent causing PML should be removed or drug concentration should be decreased by blood plasma exchange therapy.

## Case report

A 53-year-old female patient was admitted to the Neurology Emergency Department of our hospital after continuous complaints of progressive left-side weakness and tremors in the left hand over a period of two months. The patient, who was diagnosed with zona zoster two weeks prior to these complaints for which she received symptomatic treatment, had no history of any other disease or medication use. In her neurological examination, muscle strength was 4/5 in the left upper and lower extremities, and she had a moderate to high amplitude postural and intention tremor in the left hand. A cranial MRI revealed pathological patchy T2 hyperintense and T1 hypointense signals in the center of the pons and in both middle cerebellar peduncles, which was more prominent on the right side, in both parietal white matter, and in the right frontal subcortical area with no contrast enhancement or mass effect. Hyperintensity was present in these regions on a diffusion-weighted imaging (DWI) scan without any signal on the apparent diffusion coefficient sequence **(Figure 1)**. In the MR spectroscopy performed for the differential diagnosis of the mass, an increase in myoinositol and choline peaks and a decrease in N-acetylaspartate were observed. On the basis of these findings, neoplastic etiologies such as lymphoma and glioblastoma were excluded. The patient was admitted to the neurology service of the hospital with preliminary diagnoses of low-grade glioma, infectious or inflammatory etiologies, and differential diagnoses. No pathology was detected in the biochemistry examinations. Leukocyte and lymphocyte counts were normal (wbc: 6130/Ul, neu: 2600/Ul lym: 2900/Ul) and flow cytometry (of blood) showed a normal phenotypic characterisation of peripheral T lymphocytes (CD4 (T-Helper) 40.7% (32-64), CD8 (T Suppresor) 32.9% (15-46), CD4/CD8 1.24 (0,8-3,9), CD3 (T Lymphocytes) 73.6% (62-87). The HbsAg, Anti-HbcAg, Anti HCV and Anti HIV tests were negative. In the cerebrospinal fluid examination, CSF analysis showed no cells with normal protein and glucose levels. Oligoclonal band type 2 pattern and CSF IgG; 18.5 mg/dL, serum IgG; 1887 mg/dL, IgG index; 2.05 were detected. No malignant cells were found in the cytological examination. Test results for Lyme disease, VDRL or common viruses, autoimmune diseases and paraneoplastic encephalitis antibodies were all negative in both the CSF and blood analysis. A high copy number of JCV DNA (6000 copy/ml) was detected in the CSF.

Mild hypoalbuminemia and an increase in gammaglobulin were observed from the serum protein electrophoresis examination **(Table 1)**. The serum immunofixation electrophoresis test revealed high levels of IgG3, kappa and lambda light chains **(Table 2)**.

The bone marrow biopsy of the patient was normocellular and showed no signs of clonal plasma cell disease or lymphoproliferative disease. No pathological FDG uptake was detected suggesting no malignancy in the body PET scan. A comprehensive review of the systems showed no previous iatrogenic or pathological immune problems. Although positive CSF JCV titer and MR findings were highly suspicious for PML, a stereotactic biopsy of the right parietooccipital area was performed in the patient without immunosuppression. Histological analysis revealed staining of the histiocytes with CD68 and negative results for pancytokeratin and IDH-1. Microscopic examination revealed areas of histiocytic infiltration and bizarre cells with hyperchromatic large nuclei. Some of these cells contained nuclear inclusions. Immunohistochemically atypical cells were IDH1 negative, SV40, p53 and Ki-67 positive. A strong positive reaction with SV40 was obtained in oligodendroglia with enlarged hyperchromatic nuclei, and with enlarged, irregularly lobulated nuclei. These findings also supported the hystopathological diagnosis of PML. Plasmapheresis was not applied because neurological findings were stable. She started a treatment of 15 mg/day mirtazapine and was discharged from hospital. In the control cranial MRI examination performed 6 months following discharge, mild regression was detected in the existing lesions. The JCV titer measured at 12 months was 676 copies/ml in

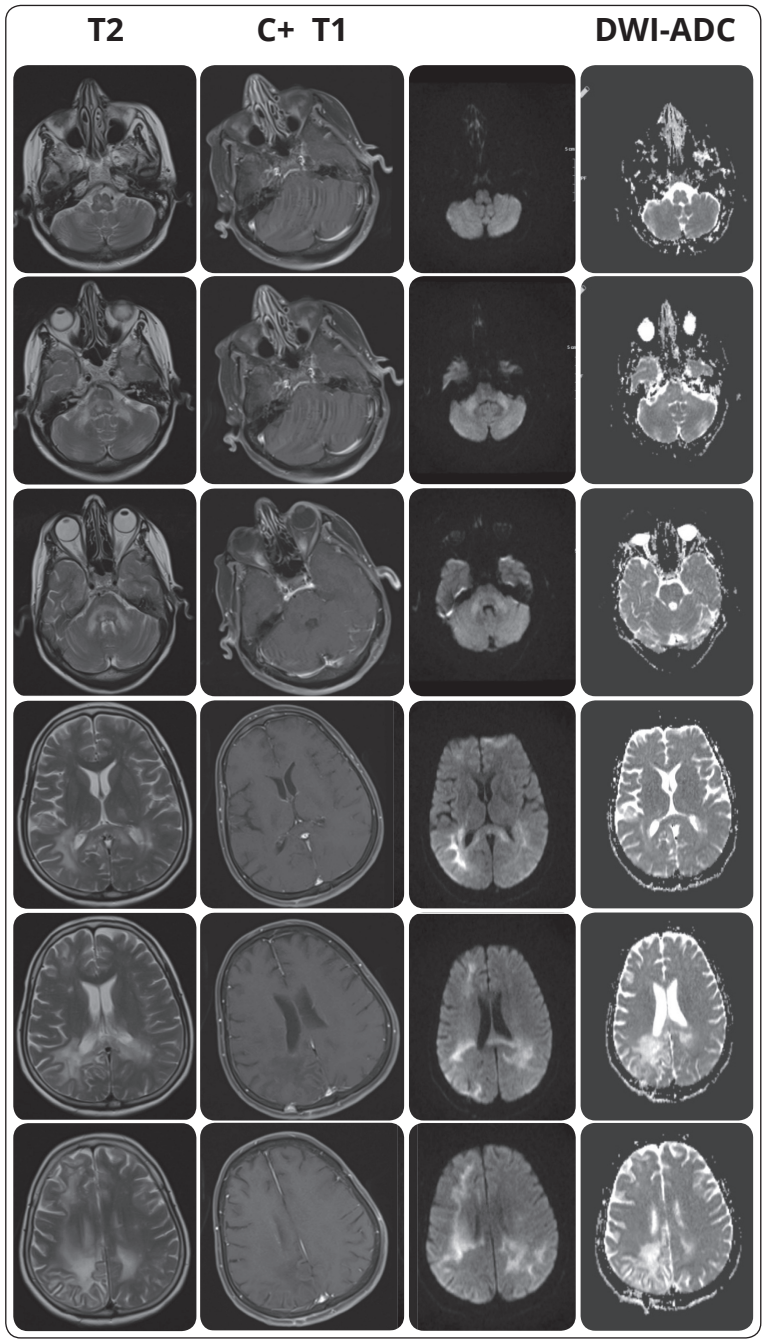


**Figure 1.** *T2 hyperintense signals in the center of the pons and in both middle cerebellar peduncles and subcortical white matter with no contrast enhancement*

the CSF and JCV was not detected in urine sample. The cranial MR examination performed a year later revealed encephalomalacia and diffuse atrophy in the right parietal area and regression was observed in pre-existing hyperintense lesions **(Figure 2)**. The hospital followed up with the patient periodically and no immunological deficit and/or malignancy were detected, and her neurological status has been stable for two years.

## Discussion

Primary JCV infection occurs mainly by respiratory or oropharyngeal exposure in adolescence and remains as a lifelong latent infection, mainly in kidney and bone marrow cells, which act as viral reservoirs[6]. JCV can be found in bone marrow and lymphoid tissue, and in precursor B, CD34+ hematopoietic progenitor to tonsillar stromal and kidney cells. In most cases of immunosuppression, the hematogenous spread plays a pivotal role in the infection of secondary regions of the reservoir tissues of neurotrophic form, which is different from this archetypal form. JCV viremia is typically suppressed by antigen-specific T cells, and the pathogenesis of PML in an immunosuppressed individual is thought to result from a deficiency of this T cell-mediated immunity. However, PML has also been reported in immunocompetent individuals, but these reports are uncommon[4]. PML is caused by productive infection of oligodendrocytes and, to a lesser extent, astrocytes.This lytic necrosis and edema around the necrosis lead to clinical features of PML[4].

Magnetic resonance imaging (MRI) is considered the gold standard for identifying and monitoring PML lesions. PML lesions have multifocal, patchy, and/or confluent hyperintensity on T2-weighted images and often have a corresponding hypointensity on T1-weighted images. Usually asymmetrical involvement is seen, while contrast enhancement and mass effects are rare[1]. Diagnosis in an immunosuppressed patient is based on clinical history, radiographic imaging, and a positive JCV PCR test in the CSF. However, it has 80% sensitivity and 95% specificity[7]. Therefore, if clinical suspicion for PML is high in a patient who is immunocompetent, a biopsy may be required for a definitive diagnosis[8]. The characteristic histopathological findings of PML include areas of focal demyelination, enlarged oligodendrocytes with intranuclear inclusions, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei, and lipid-laden macrophages[9]. The presence of JCV tissue antigens and the immunohistochemical identification of JCV DNA or SV40 positive cells suggest PML[4, 8].

Agents that inhibit the entry of JCV into cells have been used for treatment, such as Citalopram and Mir-

**Table 1.** *Serum protein electrophoresis examination*

| Total protein | 9.90 g/dL |
|---|---|
| Albumin | 47.57% |
| Alfa-1 globulin | 3.76% |
| Alfa-2 globulin | 6.85% |
| Beta-1 globulin | 6.55% |
| Beta-2 globulin | 4.03% |
| Gamma globulin | 31.23% |

**Table 2.** *Serum immunofixation electrophoresis test*

| IgA | 3,27 g/L |
|---|---|
| $IgG^3$ | 3,018 g/L |
| IgM | 2,80 g/L |
| Kappa light chains | 8 g/L |
| Lambda light chains | 3.51 g/L |

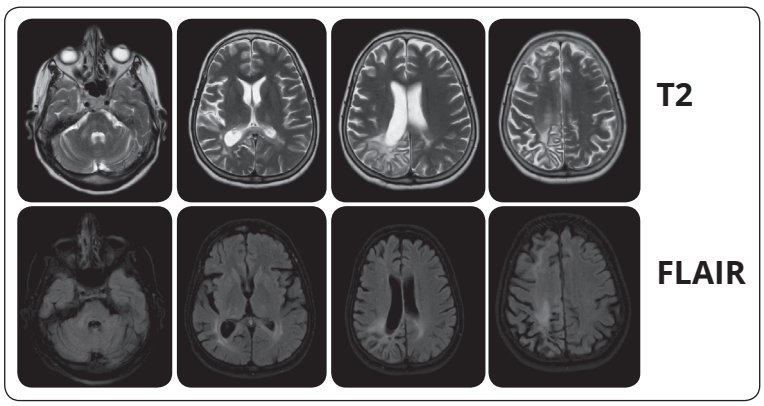


**Figure 2.** *Encephalomalacia and diffuse atrophy in the right parietal area and regression of pre-existing hyperintense lesions*

tazapine, Retrograde transport inhibitors such as Retro-2cycl, Brefeldin A, DNA replication inhibitors such as Brincidofovir, cytarabine, leflunomide, and agents such as maraviroc that block CCR5-mediated tissue inflammation, but clinical responses were not qualified to constitute a treatment algorithm[10]. Immunoreconstitution is the only approved treatment[2, 4, 8]. In vitro evidence that the 5-HT2A receptors on human glial cells may play an important role in JCV entry has led to investigations on the use of serotonin receptor antagonists in therapy[4, 10]. In many case reports, Mirtazapine, an antidepressant with α2-adrenergic, 5-HT2A and 5-HT3 receptor antagonisms crossing the blood brain barrier, has been implicated in preventing the progression of PML[11]. However, since there is no clinical study on this medication, its use is controversial and there are case reports reporting no effectiveness of 5-HT receptor blockers.

There was not known or detectable immunosuppression in the admitted patient, but the presence of shingles lesions, which is an opportunistic infection shortly before the development of a neurological deficit, raises suspicions that the patient was in a transient immunosuppressive period. However, it is thought that such a mild process that could form the basis for PML is alarming for possible future clinical scenarios.

There are limited case reports of patients who develop PML without immunosuppression. Considering the high mortality rate and lack of treatment options in immunocompetent patients with PML, this patient started mirtazapine therapy similar to what was used in several case reports with successful results[4, 12–14]. A clinically stable course is a rather atypical situation in the literature for an immunocompetent patient with PML. Because the review recently published by *Sriwastava* et al.[15] consists 22 cases, our patient is the 23rd case in the literature without immunodeficiency. In the review, clinical improvement was found in 22 patients and mirtazapine and its combinations were used in 11 of 18 study patients; in case of nine out of the 22 patients the disease was non-fatal and the rate of mirtazapine use and its combinations in this group was 6/9[15]. It is not possible to establish a definitive causal relationship with the clinical efficacy of mirtazapine, which is known to enter glial cells via 5-HT2a receptors and is used in the treatment through this mechanism, and the clinical stabilization may be the result of spontaneous immune reconstitution. The available data evaluating the efficacy of medical therapy in PML are based on the immunosuppressived population and thus this data may not be applicable to immunocompromised individuals. The exceptionality and high mortality of PML in immunocompetent patients hinder clinical research and make case reports key for evaluating outcomes. The envisaged contribution was to present a patient without immunodeficiency who was treated with mirtazapine and showed a favorable clinical course.

CONFLICT OF INTEREST – The authors declare that they have no conflict of interest.

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