Nörologlar Açısından Progresif Multifokal Lökoansefalopati (PML) ve IRIS

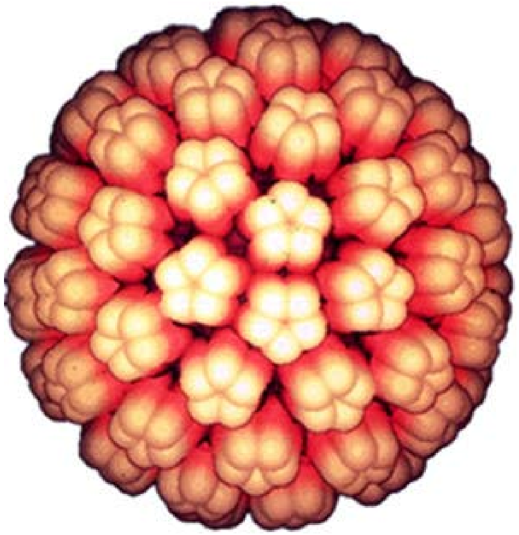
Nasıl Oluşur?

Tedavi Seçenekleri

Dr. Aslı Tuncer
Hacettepe Üniversitesi Tıp Fakültesi
Nöroloji Anabilim Dalı
Uluslararası Türk Dünyası Multipl Skleroz Kongresi
14-17 Şubat 2019

Progresif Multifokal Lökoensefalopati

- *PML* santral sinir sisteminin ağır seyirli ve demiyelinizanyon ile sonuçlanan hastalığıdır
- Polyomavirus ailesinden, çift sarmal DNA virusü olan fırsatçı JC virüs reaktivasyonuna bağlı olarak gelişmektedir
- Sıklıkla immün sistemi herhangi bir nedenle baskılanmış olan bireylerde görülmektedir



PML- İmmün Sistem

- HIV-AIDS
- Hematolojik maliniteler
- Organ transplantasyonu
- Diğer immünosupresanlar (metotreksat, siklofosfamid, azatiopurin, fludarabin…)
- monoklonal Ab kullanımı (natalizumab, rituksimab, efalizumab, alemtuzumab..)

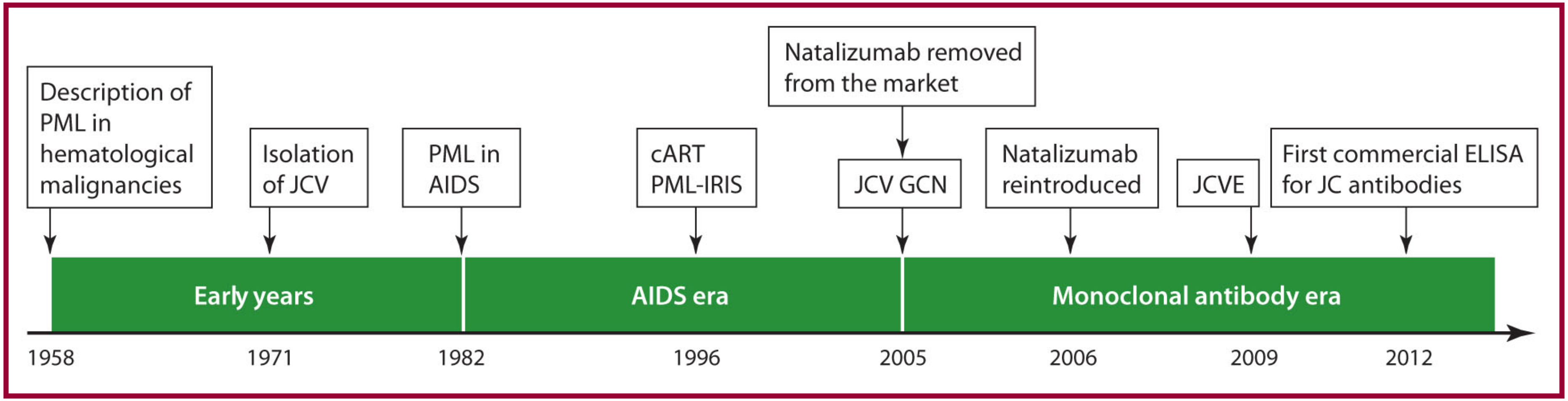
PML Tarihçe

İlk 1958’de tanılandı

- **2 KLL ve 1 Hodgkin olgusu**
  Astrom et al., 1958
- **Elektron mikroskopisi: Papovavirus virusun PML hastasında, beyin dokusundanglial hücrelerden izole edilmesi -JC virus ismi**
  Padgett et al., 1971

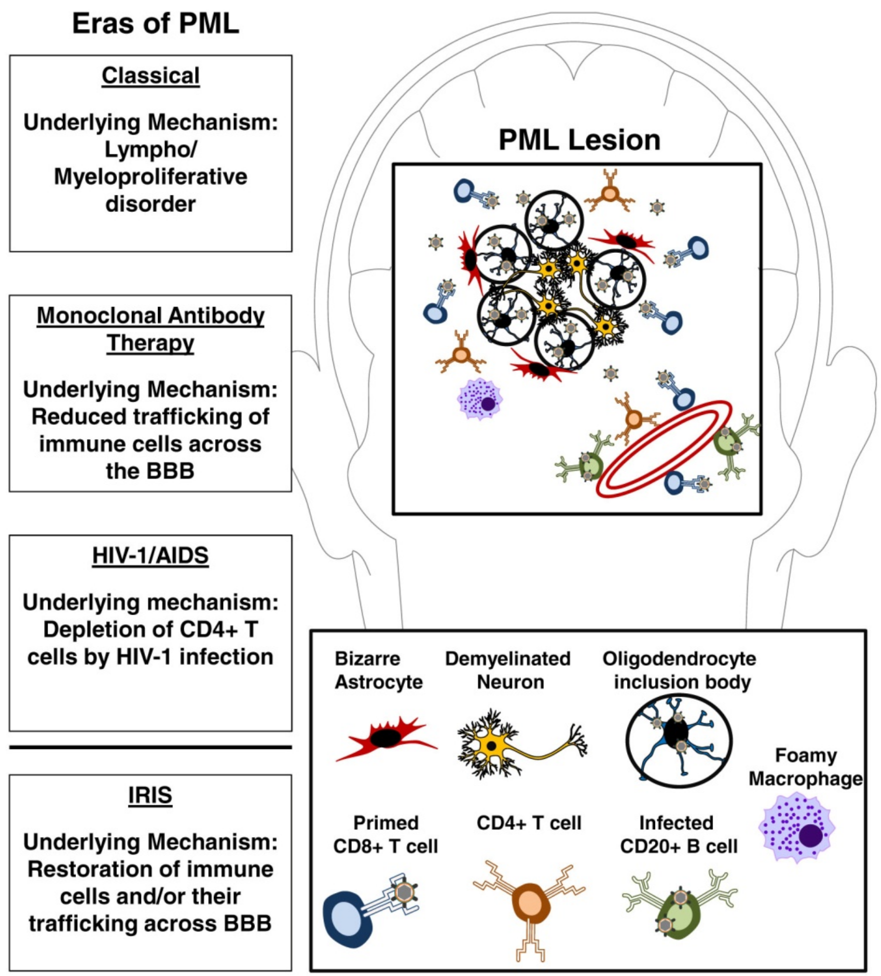
John Cunningham ailesi

Zaman İçindeki Gelişmeler...



Gheuens S, Wüthrich C, Koralnik IJ. Annu Rev Pathol Mech Dis 2013;8:189-215

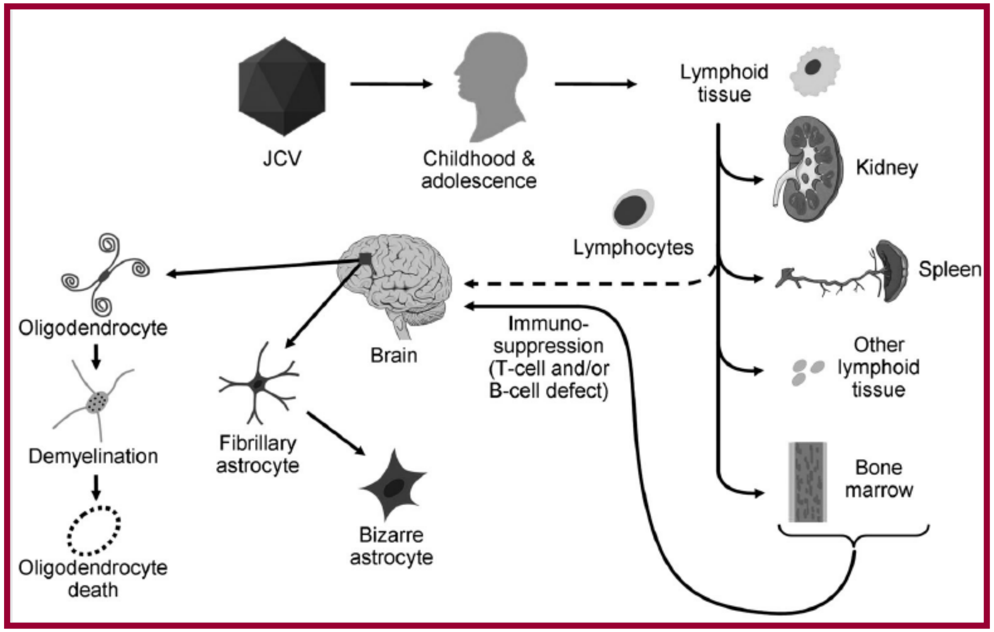
PML Lezyonunun İmmünopatolojik Özellikleri



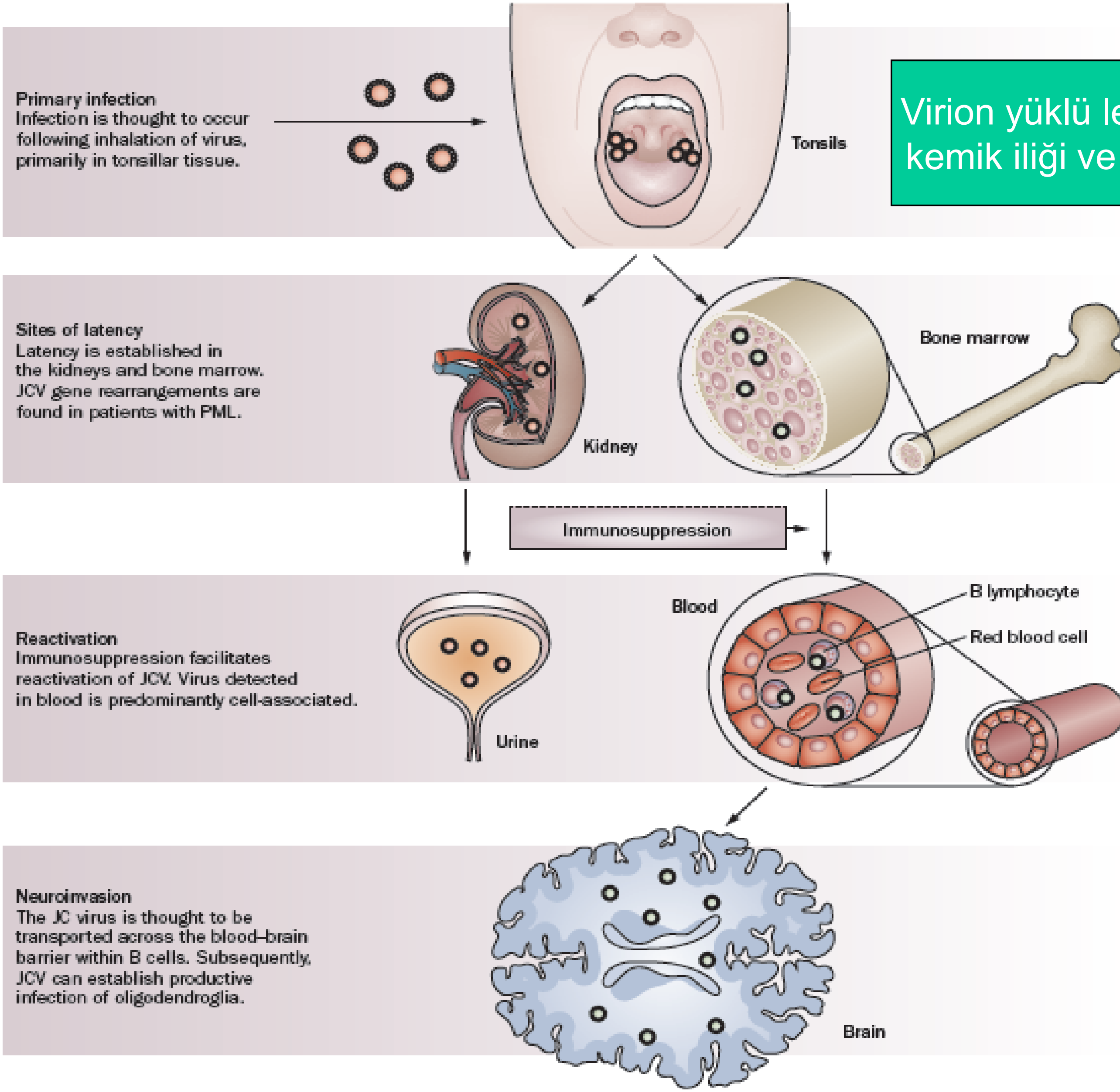
Beltrami S, Gordon J. J Neurovirol 2014;20:137-149

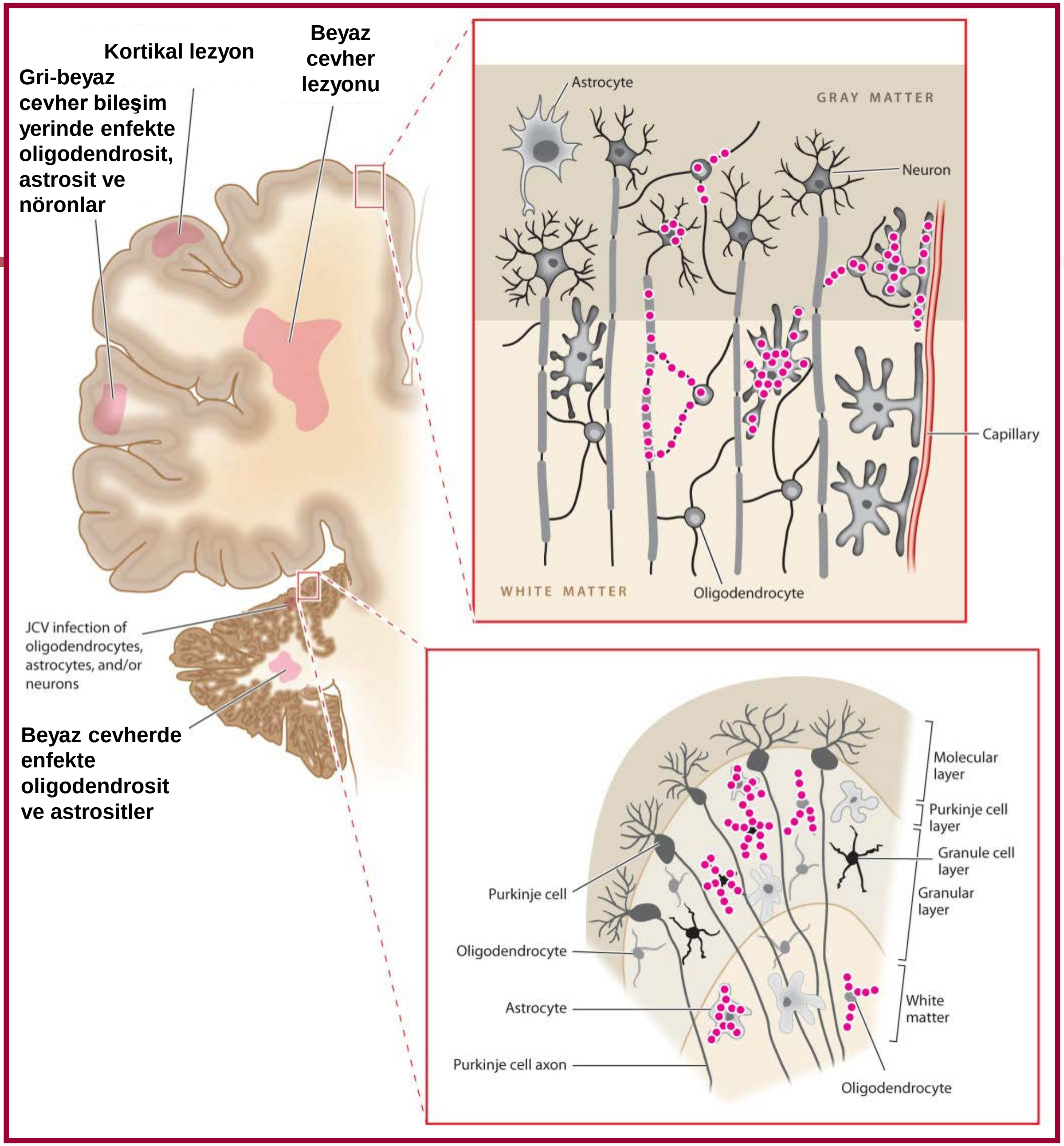
JC Virus

- **Bulaş?**
- **Respiratuar veya orofaringeal**
  - **Tonsiller dokuda** ***(Monaco et al., 1998)***
- **SSS geçiş?**
  - **İmmün baskılanmada vücutta virusun aktivasyonu**
  - **SSS'de latent virusun aktivasyonu**



Virion yüklü lenfositler tarafından kemik iliği ve böbreklere taşınma





Gheuens S, Wüthrich C, Koralnik IJ. Annu Rev Pathol Mech Dis 2013;8:189-215

Lessons Learned From Fatal Progressive Multifocal Leukoencephalopathy in a Patient With Multiple Sclerosis Treated With Natalizumab

Aaron L. Boster, MD; Jacqueline A. Nicholas, MD; Ilir Topalli, PhD; Yaz Y. Kisanuki, MD; Wei Pei, PhD; Bethanie Morgan-Followell, MD; Claudia F. Kirsch, MD; Michael K. Racke, MD; David Pitt, MD

JAMA Neurol. 2013;70(3):398-402.

A1: **Subkortikal, kortekse uzanan beyaz cevher lezyonu**

A2: **Yama tarzında kortikal demiyelinizasyon**

A3: **Normal görünümlü gri cevher**

B ve C: **CD68 ile boyanan miyelin yüklü mikroglia ve makrofajlar**

D: **Normal beyaz cevher ve kortekste mikroglia görünümü**

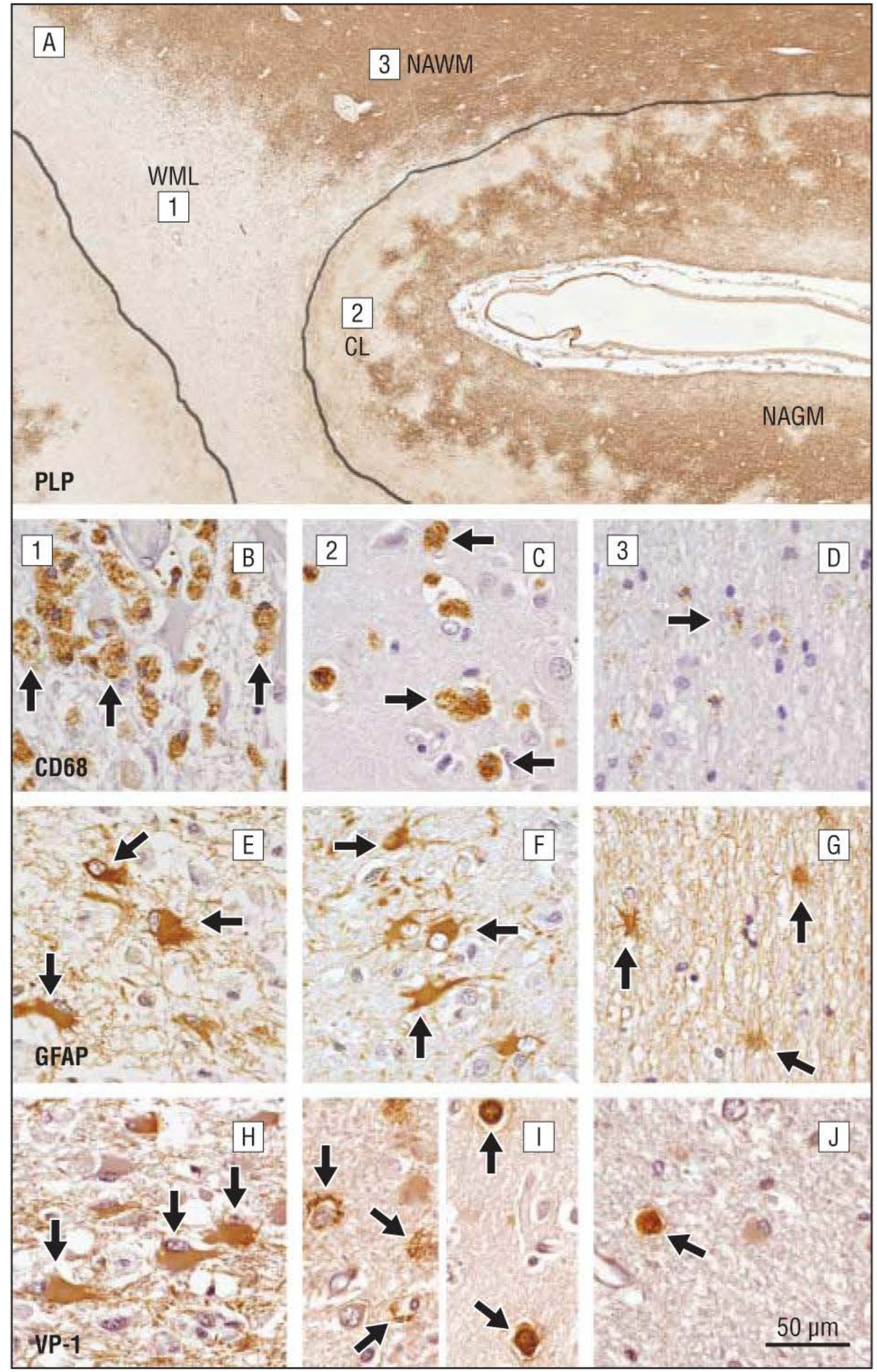
E ve F: **GFAP ile boyalı yüksek reaktif astrositler**

G: **Normal beyaz cevherde küçük, ince astrositler**

H: **JC virüs kapsit proteininin reaktif astrosit sitoplazmasındaki varlığı**

I: **Kortikal lezyonlarda kapsit proteinin nöron ve oligodendrositler içinde varlığı**

J: **Normal beyaz cevherde oligodendrositlerde kapsit protein varlığı**



JCV ile İlişkili Nörolojik Durumlar

Table 2 Overview of JC virus (JCV)-associated neurological conditions

	Classic PML	PML-IRIS	JCV GCN	JCVE	JCV meningitis
Population at risk	Immunosuppressed individuals (AIDS, transplant recipients, hematological malignancies, autoimmune disease, monoclonal antibodies)	Immune restoration (cART, discontinuation of immunosuppressive/ immunomodulatory drugs)	Same as that for classic PML	Same as that for classic PML	Unknown, possible manifestation of primary infection
Clinical features	Depend on lesion location; 18% develop seizures	Paradoxical worsening or development of new symptoms	Cerebellar syndrome (dysmetria, ataxia)	Encephalopathy and seizures	Meningismus
Imaging features	Asymmetrical subcortical white matter lesions that spread through white matter tracts	Enhancement in 50%; elevated mI/Cr, Cho/Cr, and lipid/Cr peaks on ^{1}H-MRS	Cerebellar atrophy	Cortical lesions	N/A
Histopathology	Demyelination in the white matter, the gray matter–white matter junction, and gray matter. Detection of JCV in enlarged oligodendrocytes; bizarre, gigantic astrocytes; and occasional neurons	Same as that of classic PML, with inflammatory infiltrates consisting mainly of $CD8^{+}$ lymphocytes	JCV-infected cerebellar granule cell neurons	JCV-infected cortical pyramidal neurons	N/A
Treatment	Immune restoration (cART, discontinuation of immunosuppressive drugs)	Same as that for classic PML and steroids in cases with marked swelling, mass effect, and marked neurological worsening	Same as that for classic PML	Same as that for classic PML	Same as that for classic PML

Gheuens S, Wüthrich C, Koralnik IJ. Annu Rev Pathol Mech Dis 2013;8:189-215

PML – Klinik Özellikler

PML Klinik Özellikleri

	MS	PML
Başlangıç	Akut	Subakut
Gelişim	Saatler günler içerisinde Normalde stabil Kendiliğinden tedavisiz iyileşen	Haftalar içinde İlerleyici
Tipik Klinik Tablo	Diplopi Parestezi Paraparezi Optik nörit Miyelopati	Afazi Davranışsal ve nöropsikiyatrik değişiklikler Retrokiazmal görsel bozukluklar Hemiparezi Nöbetler

PML Tanı

VIEWS & REVIEWS

PML diagnostic criteria

Consensus statement from the AAN Neuroinfectious Disease Section

Joseph R. Berger, MD
Allen J. Aksamit, MD
David B. Clifford, MD
Larry Davis, MD
Igor J. Koralnik, MD
James J. Sejvar, MD
Russell Bartt, MD
Eugene O. Major, PhD
Avindra Nath, MD

Certainty of PML diagnosis	Compatible clinical features	Compatible imaging findings	CSF PCR for JC virus
Definite	+	+	+
Probable	+	–	+
	–	+	+
Possible	+	+	–/ND
	–	–	+
Not PML	–	–	–
	+	–	–
	–	+	–

Tanı Kriterleri

Table 1 Progressive multifocal leukoencephalopathy (PML) diagnosis criteria

PML diagnosis subcategory	Clinical and radiological findings consistent with PML
Histologically confirmed PML	Demyelination and detection of JCV protein by IHC, or JCV DNA by ISH or PCR, in brain biopsy or autopsy
Virologically confirmed PML	Detection of JCV DNA by PCR in CSF
Possible PML	No detection of JCV DNA by PCR in CSF and absence of other infections or tumors

Gheuens S, Wüthrich C, Koralnik IJ. Annu Rev Pathol Mech Dis 2013;8:189-215

PML – MRG Özellikleri

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

Table 1. Overview of the value of different pulse sequences in the diagnosis and PML.

MRI pulse sequence	Imaging feature
FLAIR	Most sensitive sequence for PML lesion detection
	Focal or multifocal white matter lesions
	Perivascular spread
	Cortical gray matter involvement
T2-weighted	Microcystic lesions ("milky way appearance")
	Cavitations, vacuoles
	Perivascular spread
	Deep gray matter lesions
T1-weighted without contrast	Cortical laminar necrosis (linear hyperintensity)
T1-weighted with contrast	Inflammatory PML lesions: punctate, linear
	PML-IRIS manifestations: progressive, confluent, with associated edema and mass effect
DWI	Acute/active demyelination

DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion-recovery; IRIS: immune reconstitution inflammatory syndrome; MRI: magnetic resonance imaging; PML: progressive multifocal leukoencephalopathy.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

En Önemli Sekanslar

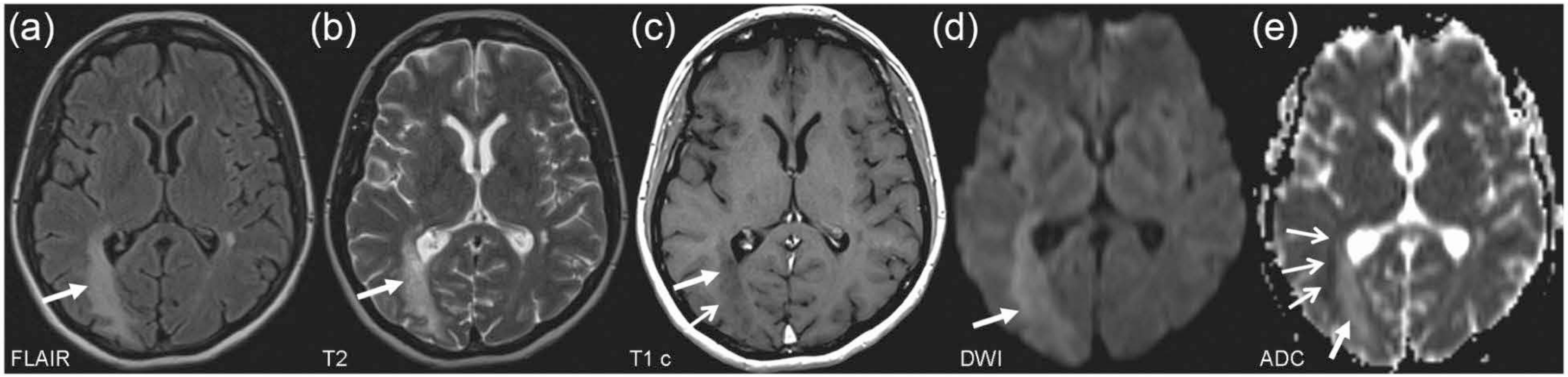


Figure 2. The use of a multisequence protocol in the diagnosis of PML.
Axial FLAIR (a), T2-weighted turbo (fast) spin echo (b), contrast-enhanced T1-weighted (c), high B-value (B1000) DWI (d), and the corresponding ADC map (e) demonstrating a classical PML lesion (closed-head arrow) in the right parietal lobe of an MS patient treated with natalizumab. The lesion shows the typical appearance and location in the subcortical white matter filling out the gyrus. FLAIR is more sensitive regarding the assessment of the PML lesion compared with the T2-weighted image. The lesion does not show any contrast enhancement. Central parts of the lesion show a low T1 signal intensity suggestive of severe myelination whereas other (peripheral) parts of the lesion are isointense or slightly hypointense ((c), open-head arrow). On the DWI, the major part of the lesion is hyperintense with a corresponding hyperintense signal on the corresponding ADC map. Only the peripheral part of the lesion shows low ADC values, suggesting acute demyelination with swelling of astrocytes and oligodendrocytes ((e), open-head arrow).
PML: progressive multifocal leukoencephalopathy; FLAIR: fluid-attenuated inversion recovery; MS: multiple sclerosis; ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

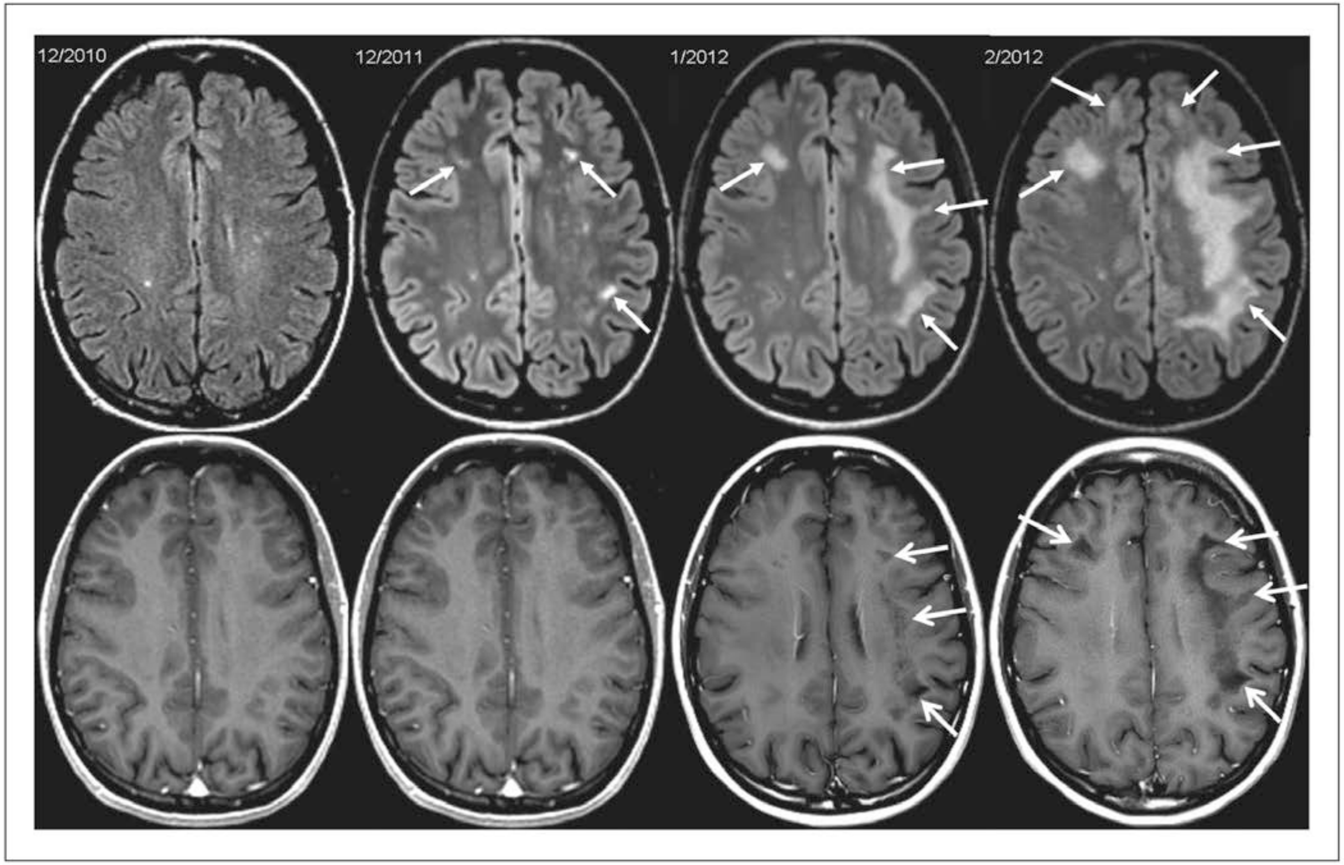


Figure 3. PML lesion manifestation and evolution in the white matter.
Axial FLAIR (top row) and contrast-enhanced T1-weighted (bottom row) MR images of an MS patient treated with natalizumab who developed PML in December 2011. Compared with the baseline scan of December 2010, PML presented as focal white matter lesions mimicking MS (closed-head arrows). During follow-up the lesions show local growth but also a spreading through the white matter resulting in a large confluent white matter lesion in the left hemisphere. On the contrast-enhanced T1-weighted images, the progressive demyelination is reflected by the progressive decrease of T1 signal intensity (hypointensity).
FLAIR: fluid-attenuated inversion recovery; MR: magnetic resonance; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

Multiple Sclerosis Journal
19(14) 1826–1840

‘milky way’

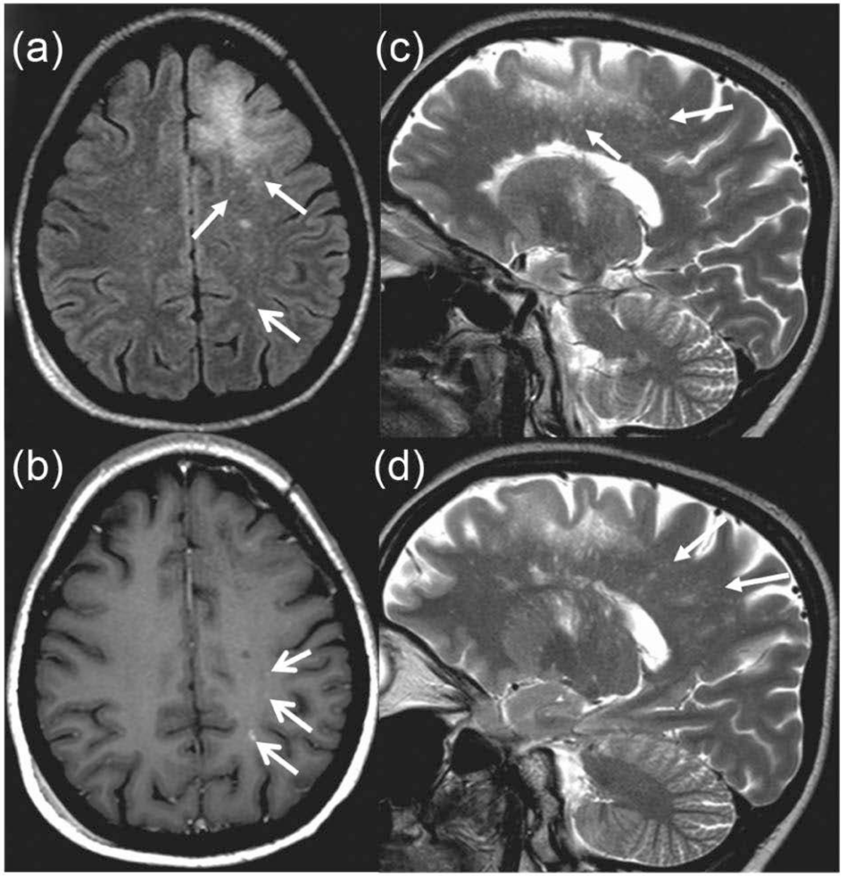


Figure 4. Microcystic appearance of PML lesions.
Axial FLAIR (a), contrast-enhanced T1-weighted (b) and sagittal T2-weighted MR images (c, d) demonstrating a PML lesion in the left frontal lobe of an MS patient treated with natalizumab. Posterior from the subcortical lesion, small lesions with a perivascular distribution pattern are visible (closed-head arrows). Some of these lesions show contrast-enhancement ((b), open-head arrows). The abundance of these small punctiform lesions within the PML lesion and in the vicinity of the PML lesion becomes more obvious on the sagittal T2-weighted images resembling scattered microcysts, hence the term “milky way appearance.”
FLAIR: fluid attenuated inversion recovery; MR: magnetic resonance; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

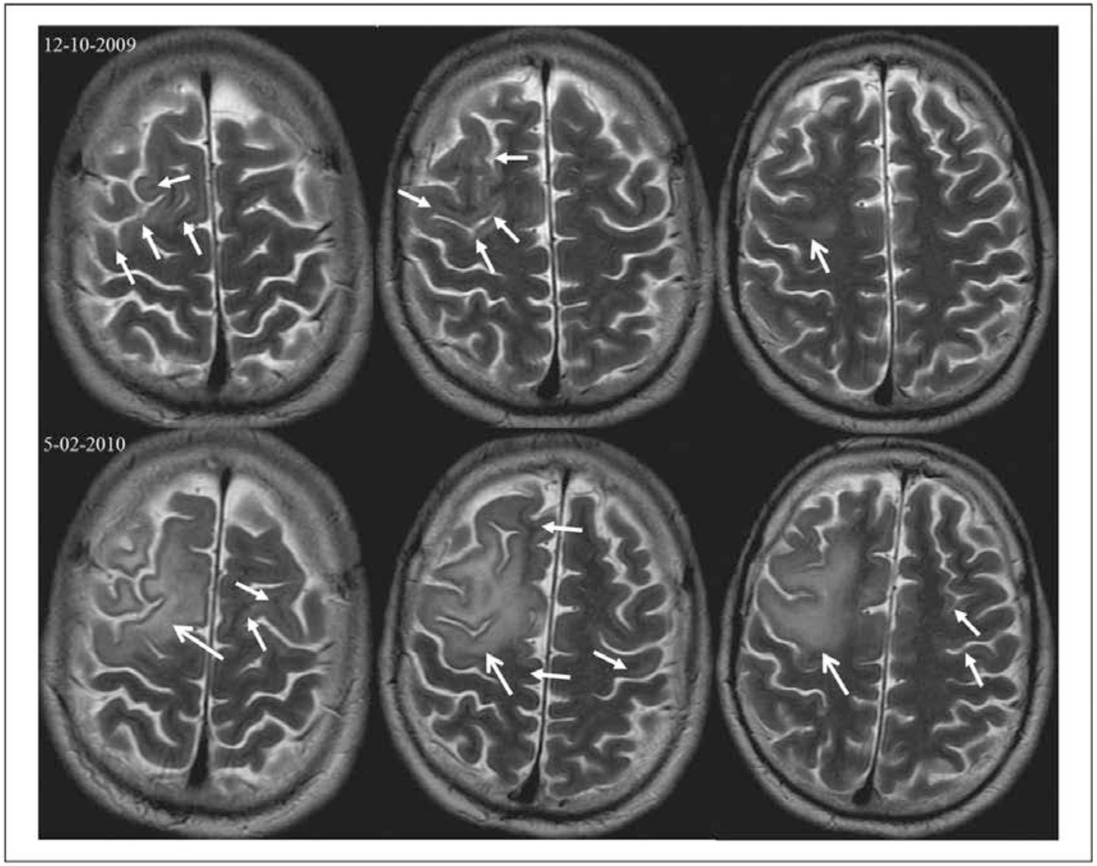


Figure 5. Cortical gray matter PML manifestations and lesion evolution.
Axial T2-weighted images in the acute stage (October 12, 2009) of a natalizumab-associated PML patient showing PML lesion manifestations primarily starting in the cortical gray matter of the right frontal lobe (closed-head arrows) and to a lesser extent in the adjacent white matter (open-head arrow). During follow-up (February 5, 2010) the lesion locally expands and infiltrates the adjacent juxtacortical and deep white matter (open-head arrows). In addition, new lesions in the cortical gray matter of the contralateral frontal lobe occur (closed-head arrows).
PML: progressive multifocal leukoencephalopathy.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

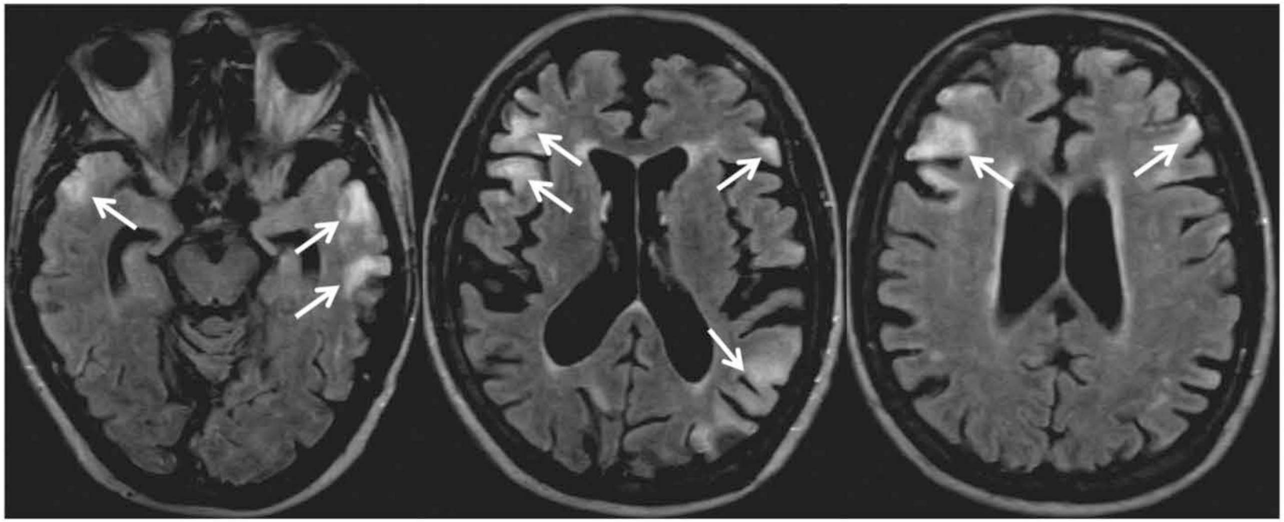


Figure 6. Cortical PML phenotype.
Axial FLAIR images demonstrating the cortical gray matter PML involvement in a patient with natalizumab-associated PML (arrows). Please note the widespread PML lesions are almost exclusively located in the cortical gray matter and juxtacortical white matter whereas deep white matter structures are not involved.
PML: progressive multifocal leukoencephalopathy; FLAIR: fluid-attenuated inversion recovery.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

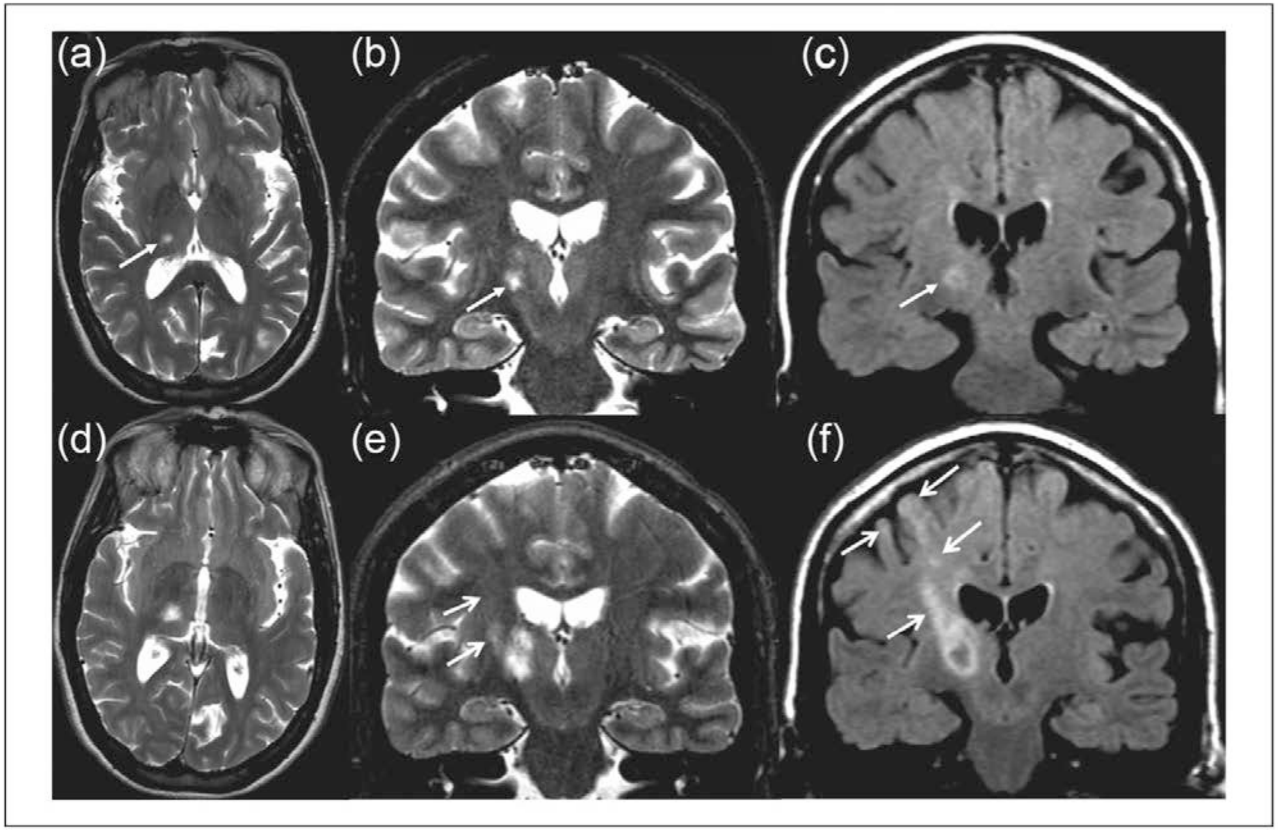


Figure 7. Deep GM PML lesion with white matter spreading.
Axial ((a), (d)) and coronal T2-weighted images ((b), (e)) and coronal FLAIR images ((c), (f)) obtained in a patient with natalizumab-associated PML. In the asymptomatic stage (top row, (a)–(c)), a new small focal lesion was identified in the right thalamus (closed-head arrows) and misinterpreted as a subacute lacunar infarct. During follow-up three months later (bottom row, (d)–(f)), the lesions expanded into the adjacent white matter grew along the cortico-spinal tract centrally reaching and involving the cortical gray matter (open-head arrows).
GM: gray matter; PML: progressive multifocal leukoencephalopathy; FLAIR: fluid-attenuated inversion recovery.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

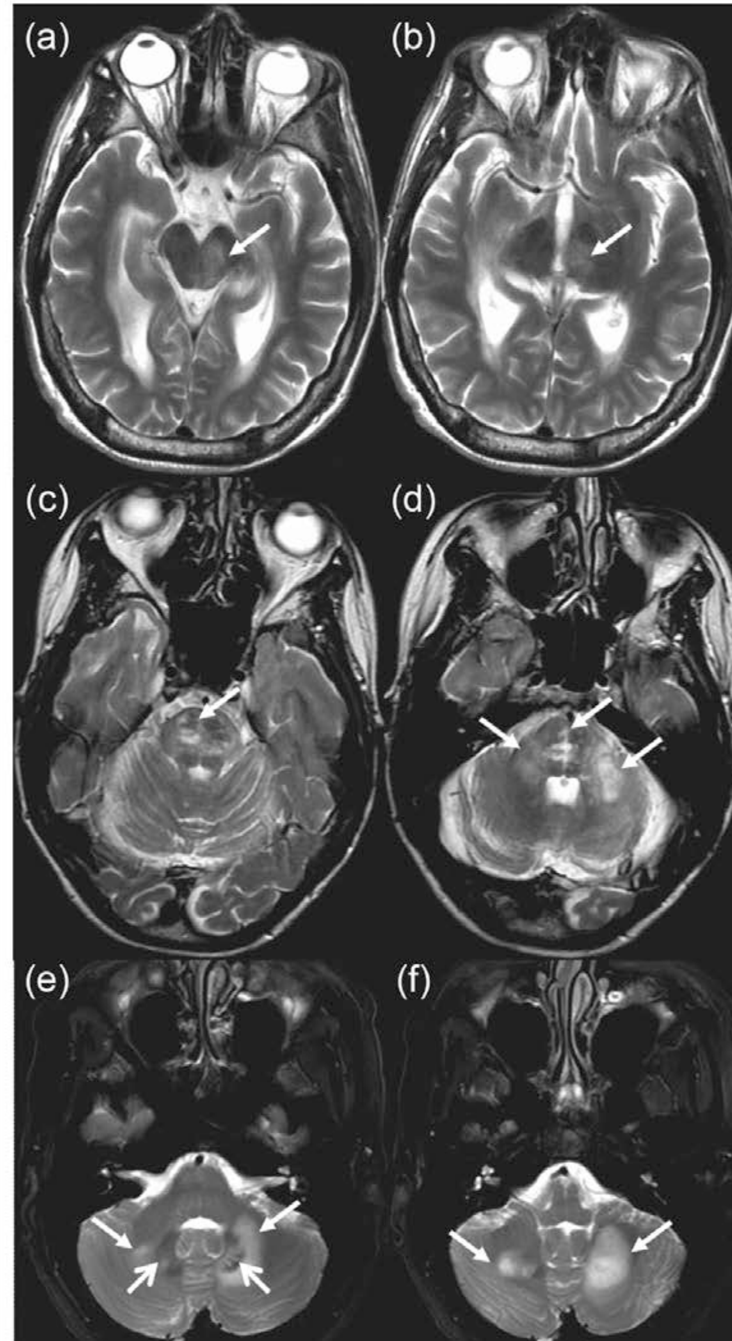


Figure 8. Examples of infratentorial PML lesion manifestations. Axial T2-weighted MR images of three patients ((a)–(f)) with natalizumab-associated PML presenting with infratentorial lesions in the acute PML stage. (a), (b): A lesion located in the left thalamus is spreading into the left mesencephalon (cerebral peduncle). (c), (d): multifocal PML lesions in the posterior fossa located in the pons (brachium pontis) and in both middle cerebellar peduncles. (e), (f): Lesion located in the cerebellar hemispheres (closed-head arrow) also affecting the dentate nucleus (open-head arrows).
PML: progressive multifocal leukoencephalopathy; MR: magnetic resonance.

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

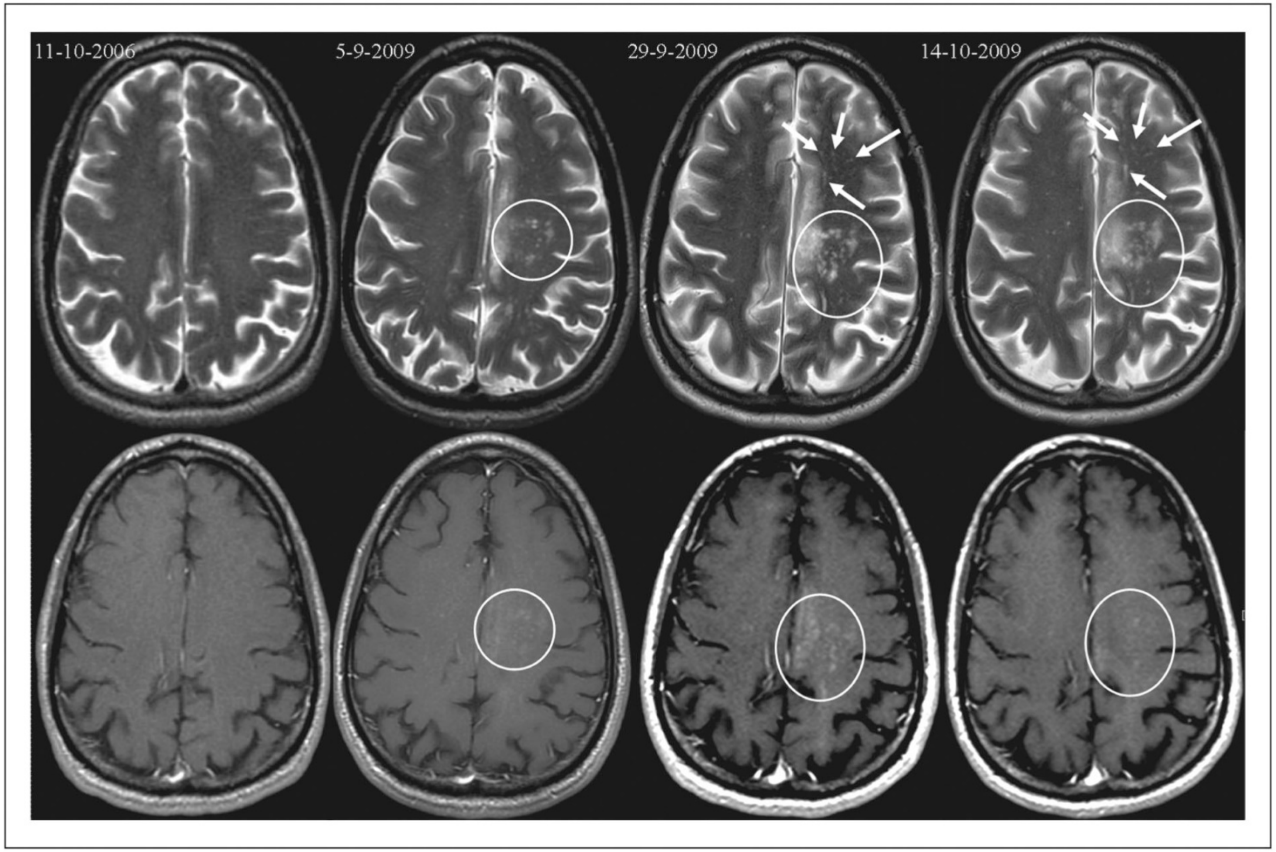


Figure 9. Perivascular inflammation in PML.
Axial T2-weighted (top row) and gadolinium-enhanced T1-weighted MR images of a patient who developed a perivascular inflammation pattern in natalizumab-associated PML. Compared with the baseline scan (June 11, 2006), the leading finding at the acute PML stage (September 5, 2009) was a group of small lesions in the deep white matter of the left hemisphere (white circle) with a perivascular distribution pattern and contrast enhancement. On follow-up (September 29, 2009), the lesions and the enhancement progressed and new lesions were observed in other areas such as the left frontal lobe (white closed-head arrows). After plasma exchange and corticosteroid treatment the contrast enhancement regressed partially (October 14, 2009).
PML: progressive multifocal leukoencephalopathy; MR: magnetic resonance.

PML – İlaçlar

PML ile İlişkisi Bildirilmiş Olan Tedavi Ajanları

Classes of agents associated with progressive multifocal leukoencephalopathy (PML)

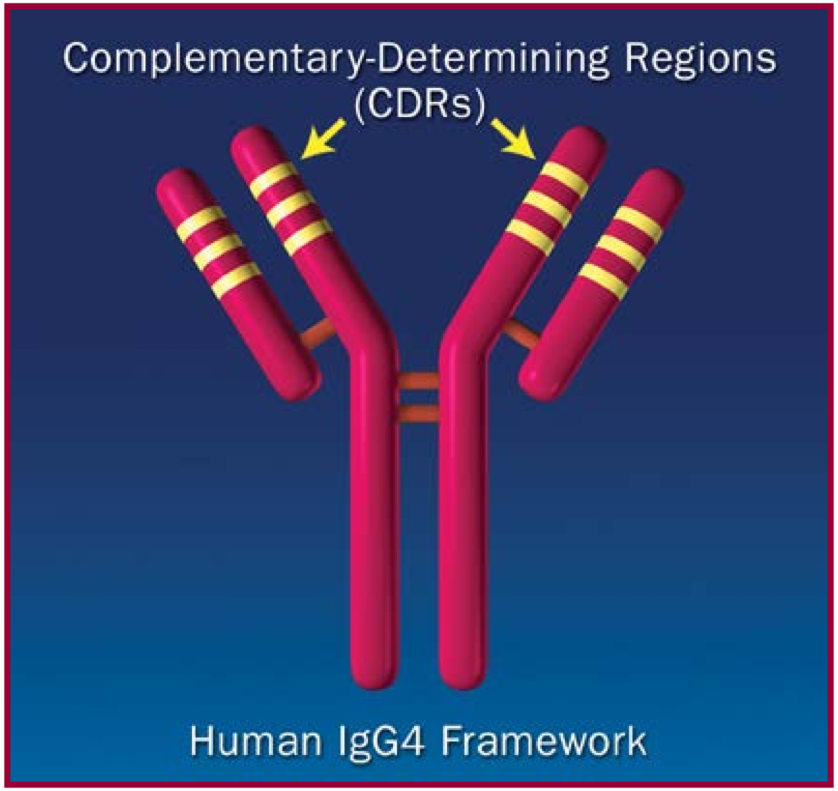
Therapeutic agent	Underlying condition previously associated with PML?	Latency from initiation of therapeutic agent to PML?	Risk of developing PML?
Class 1	No	Long	High
Natalizumab	MS, Crohn's disease	>8 months, peaking at 24 months	Depends on JC virus antibody status, duration of administration, and prior immuno-suppressants. Ranges from 1:1000 in 1–24 months in JC virus-seropositive subjects and no prior immunosuppressants, to >1:100 after 24 months in JC virus-seropositive subjects with prior immunosuppressant use
Efalizumab	Psoriasis		
Class 2	Yes	No latency. PML arises stochastically after beginning drug	Infrequent
Rituximab	Lymphoproliferative disorders, rheumatoid arthritis, systemic lupus erythematosus, AIDS	None	1:30 000
Mycophenolate mofetil	Solid-organ transplants, systemic lupus erythematosus, and other autoimmune diseases	None	?
Brentuximab vedotin	Hodgkin's disease	None	?

Berger JR. Handbook of Clinical Neurology, Vol. 123 (3rd series) 2014; Chapter 17

Natalizumab: SAM İnhibitörü

α4-integrin antagonisti

- **Human IgG4 yapısı**



PML ile İlişkisi Bildirilmiş Olan Tedavi Ajanları

Table 1. Incidence of PML in MS DMTs.

DMT	Cases of PML	PML patient age (years)
Natalizumab	763 in >181,300 patients[a]	15–73
Fingolimod	19 in >225,000 patients[b]*	34–71
Dimethyl fumarate	5 in >270,000 patients[a]*	54–66
Ocrelizumab	0 in >40,000 patients[c]*	
Teriflunomide	0 in >71,000 patients[d]*	
Alemtuzumab	0 in >18,400 patients[d]*	

PML: progressive multifocal leukoencephalopathy; MS: multiple sclerosis; DMT: disease-modifying therapy;
*Cases of PML not attributable to prior natalizumab exposure.
[a]Biogen internal data file.
[b]Novartis internal data file.
[c]Genentech internal data file.
[d]Sanofi Genzyme internal data file.

Millis EA., . Multipl Sclerosis Journal, 2018

PML Risk

- **PML için risk oluşturan faktörler:**
  - **Anti-JCV antikor varlığı**
  - **Natalizumab öncesi immünsupresif tedavi kullanmak**
  - **Natalizumab kullanım süresi (özellikle >2 yıl)**

Türkiye'de PML Vakaları

Hasta No	Tedavi başlangıcı	Tedavi sonlanım tarihi	IS Kullanımı	İlk Bulgu Tarihi	PML Tanısı	Takip Bilgisi
1	1 Ekim 2009	10 Mayıs 2012	Ø	25 Ağustos 2012	30 Kasım 2012 (19 kopya/ml)	Kliniğinde ayaktan takip ediliyor. Kasım 2014 de EDSS 1.0, Karnofsky 100.
2	1 Mart 2012	1 Nisan 2014	Ø	8 Nisan 2014	25 Mayıs 2014 (48119 kopya/ml)	28 Şubat 2015 tarihinde kaybedildi.
3	1 Eylül 2010	13 Haziran 2014	Ø	28 Haziran 2014	16 Temmuz 2014 (11200 kopya/ml)	14 Eylül 2014 tarihinde kaybedildi.
4	1 Kasım 2012	1 Kasım 2014	Azatioprine 50 mg (2x2) Nisan 2010 – Eylül 2012	5 Ocak 2015	20 Ocak 2015 (384000 kopya/ml)	21 Mart 2015 tarihinde kaybedildi.
5	Ocak 2007	Mart 2013	Azatiopirin (1998 – 1999)	27 Nisan 2013	30 Nisan 2014 (38 kopya/ml)	Kliniğinde ayaktan takip ediliyor. Kasım 2014 de EDSS 6.0 ve Karnofsky 70.

Risk Değerlendirmede Belirleyiciler:
Anti-JCV Antikorları, Daha Önce İmmünsupresif İlaç Kullanımı, Tedavi Süresi

Anti-JCV Antibody Status

Negative

0.1/1000
95% CI 0.01-0.35

Positive

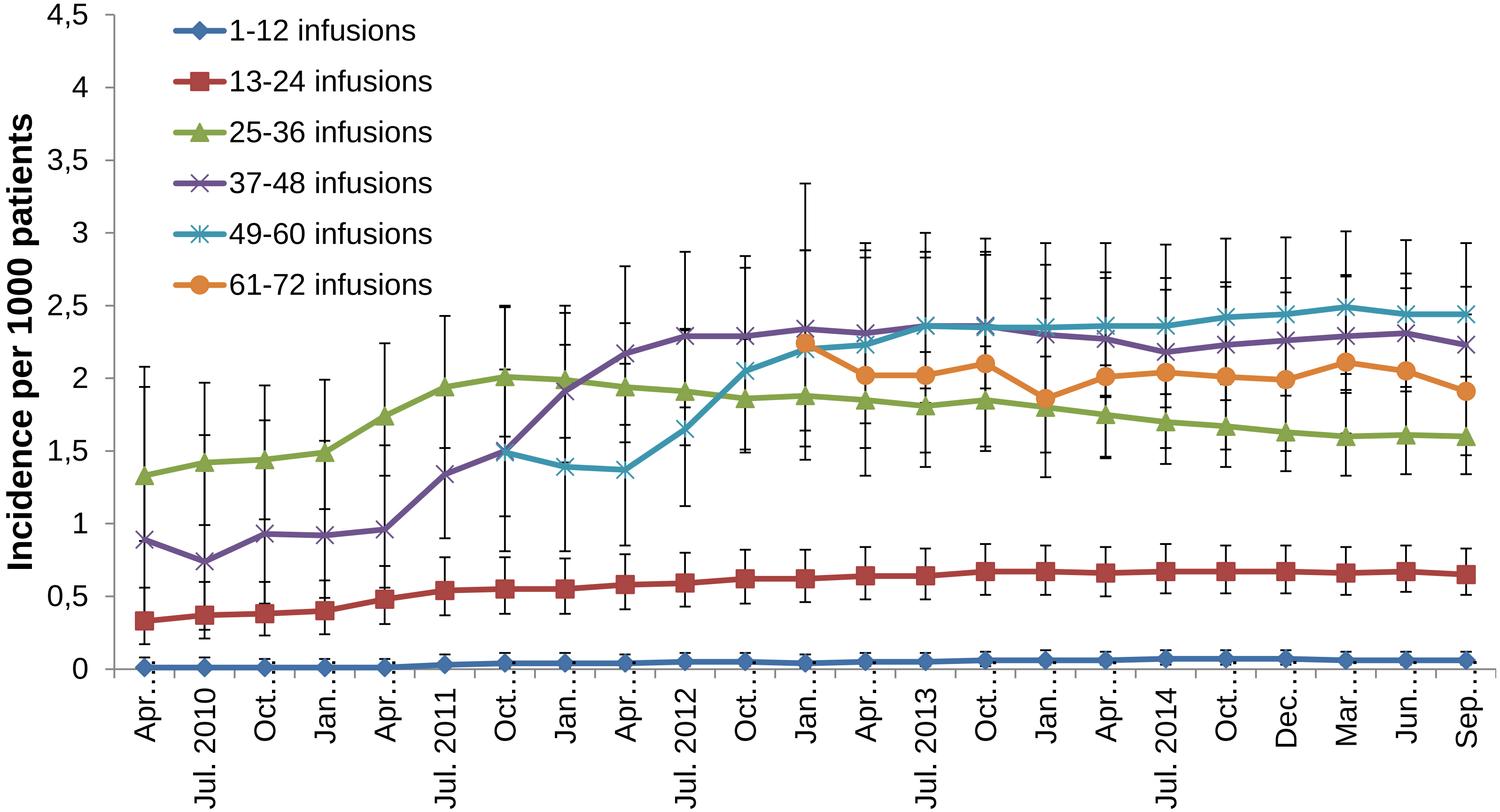
Prior IS Use

No **Yes**

Natalizumab Exposure	No Prior IS Use	Prior IS Use
1–24 months	1/1000	2/1000
25–48 months	5/1000	11/1000
49-72 months	6/1000	9/1000

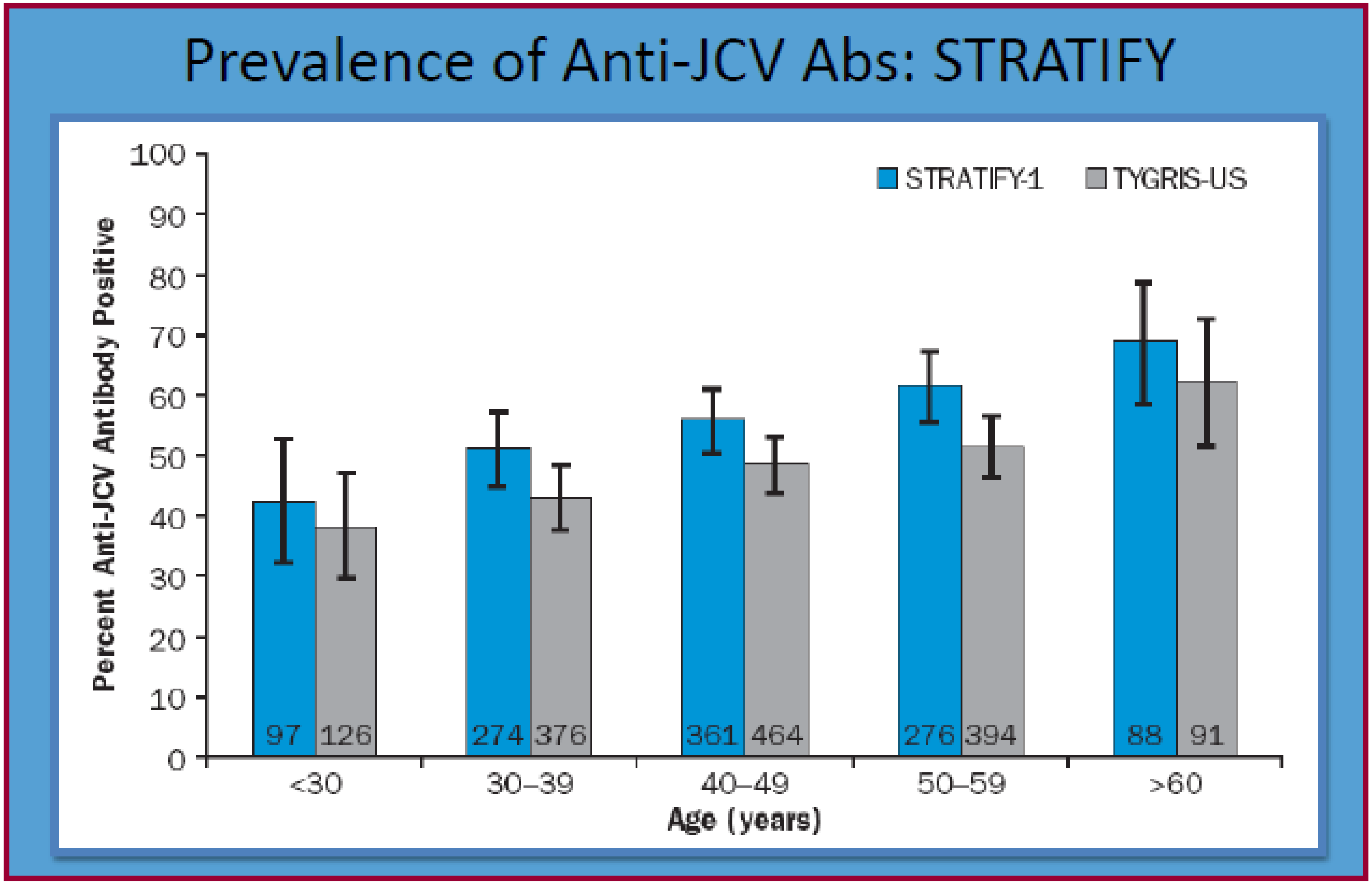
The PML risk estimates are based on post-marketing data from approximately 125,000 TYSABRI exposed patients.
Data beyond 6 years of treatment are limited.

Tedavi Süresi – PML Riski



Incidence estimates by treatment epoch are calculated based on natalizumab exposure and confirmed cases of PML. Data are from the specified month as indicated. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to natalizumab at each timepoint (e.g., for 25 to 36 infusions, the number of all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time)

JCV Pozitifliği



Journal of Experimental and Clinical Medicine

Clinical Research

doi: 10.5835/jecm.omu.31.01.006

Anti-John Cunningham Virus antibody prevalence in multiple sclerosis patients in Turkey

Mefkure Eraksoy[a*], Kadriye Agan[b], Fikri Ak[c], Omer Anlar[d], Belgin Petek Balci[e], Cavit Boz[f], Yahya Celik[g], Seref Demirkaya[h], Husnu Efendi[i], Muhtesem Gedizlioglu[j], Dilek Gunal[b], Hulya Aydin Gungor[k], Nihal Isik[l], Egemen Idiman[m], Rana Karabudak[n], Asli Kurne[n], Munife Neyal[o], Serkan Ozakbas[m], Ozgul Ekmekci Ozbay[p], Cemal Ozcan[q], Nese Subutay Oztekin[c], Musa Ozturk[r], Sabahatin Saip[s], Aksel Siva[s], Aysun Soysal[r], Ozlem Taskapilioglu[p], Murat Terzi[t], Omer Faruk Turan[u], Recai Turkoglu[v], Nezih Yucemen[w], Canan Yucesan[w], Ayse Nur Yuceyar[p], Yasar Zorlu[x], Cunay Ulku[y], Huseyin Dib[y], Deniz Uren[y]

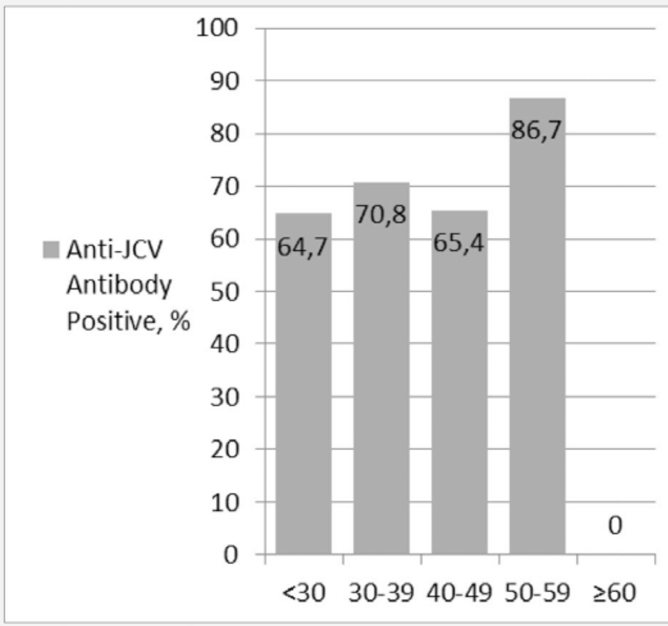


Fig. 1. Seroprevalance among the age groups. p value across age categories was determined by Fisher's Exact Test (p=0.218).

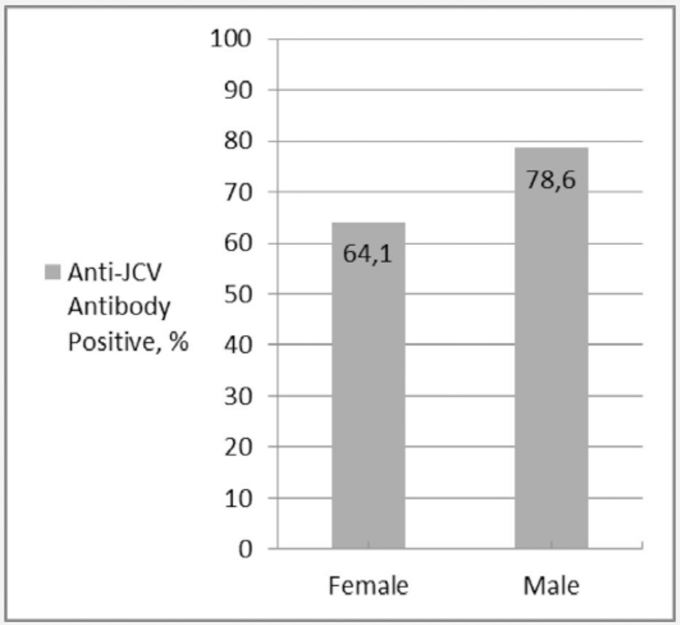


Fig. 2. John Cunningham Virus antibody positivity is higher in men than in women (p<0.05).

İndeks /Tahmini PML Riskleri

Index	PML risk (95% CI) per 1000 patients (no prior IS use)		
	1-24 months	25-48 months	49-72 months
≤0.9	0.1 (0-0.41)	0.3 (0.04-1.13)	0.4 (0.01-2.15)
≤1.1	0.1 (0-0.34)	0.7 (0.21-1.53)	0.7 (0.08-2.34)
≤1.3	0.1 (0.01-0.39)	1.0 (0.48-1.98)	1.2 (0.31-2.94)
≤1.5	0.1 (0.03-0.42)	1.2 (0.64-2.15)	1.3 (0.41-2.96)
>1.5	1.0 (0.64-1.41)	8.1 (6.64-9.8)	8.5 (6.22-11.38)

Önceki IS Kullanımı Olmayan/JC+

PML'de Sağkalım İçin Belirteçler

- Genç yaşta tanı
- Tanı öncesi sınırlı fiziksel özürlülük
- Tanı sırasında düşük JC virüs yükü
- MRG bulgularının sınırlı olması

Erken PML Bulguları

TABLE 1: Recommendations for the Diagnosis of Early PML in Natalizumab-Treated Multiple Sclerosis Patients

Features	Characteristics
Location	[a]Subcortical location is the prime site, thereby involving U-fibers; cortex and basal ganglia are often involved; often bilateral
Size	Usually >3cm
Borders	Sharp toward the gray matter, ill defined toward the white matter
Mode of extension	Lesions increase in size and new lesions appear
Mass effect	No mass effect in small or large lesions
T2W images	Always hyperintense
T1W images	[a]Typically hypointense; no reversion of signal intensity; hyperintensity is suggestive of PML-IRIS
FLAIR	Always hyperintense; better appreciated than on T2W images
DW images	[a]Always hyperintense; in larger lesion there is a hyperintense rim at the lesion's edge
Perilesional	[a]Small, punctate T2-hyperintense lesions in the immediate vicinity of the main lesion are often present
Enhancement	Frequent enhancement, punctate and/or rimlike
Atrophy	No atrophy in the early phase

[a]Features especially helpful in the identification of small PML lesions.
DW = diffusion-weighted; FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy; T1W = T1-weighted; T2W = T2-weighted.

Yousry TA, et al. Ann Neurol 2012;72:779-787

PML Semptomları

Davranışsal-bilişsel ve motor semptomlar

PML symptoms, n (%)*	Asymptomatic PML (n=8)	Symptomatic PML (n=342)
Cognitive/behavioral	5 (55.6)	176 (51.5)
Motor	3 (33.3)	163 (47.7)
Speech	1 (11.1)	100 (29.2)
Visual	0 (0)	68 (19.9)
Cerebellar	1 (11.1)	64 (18.7)
Seizure	1 (11.1)	27 (7.9)
Sensory	1 (11.1)	23 (6.7)

- PML symptoms observed in asymptomatic patients who later became symptomatic and in patients symptomatic at PML diagnosis

*Symptoms reported at a later stage after diagnosis in asymptomatic patients and at diagnosis in symptomatic patients; each patient may have more than one symptom. Based on 372 natalizumab-PML cases confirmed as of June 5, 2013.
PML, progressive multifocal leukoencephalopathy.
Dong-Si T et al. *Annals of Clinical and Translational Neurology.* 2014. [in press]

Fonksiyonel Durum

Zaman içerisinde asemptomatik PML'lerde daha az fonksiyonel özürlülük izlenmektedir

	Asymptomatic PML patients (n=17)	Symptomatic PML patients (n=107)	*P* value
EDSS score			
Pre-PML	3.2 (n=21)	3.7 (n=179)	0.336
At diagnosis	**4.1 (n=11)**	**5.4 (n=193)**	**0.038**
At 6 months	**4.9 (n=11)**	**6.6 (n=87)**	**0.007**
At 12 months	5.1 (n=6)	6.5 (n=59)	0.169
KPS score			
Pre-PML	84.0 (n=10)	81.1 (n=97)	0.475
At diagnosis	**70.0 (n=11)**	**53.8 (n=122)**	**0.008**
At 6 months	**71.5 (n=10)**	**47.1 (n=108)**	**<0.001**
At 12 months	56.0 (n=5)	46.6 (n=67)	0.178

P value from Mann-Whitney-Wilcoxon test.

- Asymptomatic PML patients experienced significantly less functional disability at diagnosis and 6 months post-PML diagnosis compared with symptomatic PML patients

Based on 372 natalizumab-PML cases confirmed as of June 5, 2013.
EDSS, Expanded Disability Status Scale; KPS, Karnofsky Performance Scale; PML, progressive multifocal leukoencephalopathy
Dong-Si T et al. *Annals of Clinical and Translational Neurology*. 2014. [in press]

PML Sağkalım

Outcome	Asymptomatic PML (n=30)	Symptomatic PML (n=342)	All PML (n=372)
Survival, n (%)	29 (96.7)	258 (75.4)	287 (77.2)
Death, n (%)	1 (3.3)*	84 (24.6)	85 (22.8)
Median (range) duration of follow-up, months	13.9 (3.4-26.6)	8.7 (0-34.7)	

*Death was reported as suicide caused by depression that was secondary to increasing disability and PML sequelae.

- The median time from PML diagnosis to death in symptomatic patients (n=78; data unavailable for 6 patients) was 2.3 (0.07-35.1) months

.
Based on 372 natalizumab-PML cases confirmed as of June 5, 2013.
PML, progressive multifocal leukoencephalopathy.
Dong-Si T et al. *Annals of Clinical and Translational Neurology.* 2014. [in press]

Radiology: Volume 000: Number 0—■ ■ ■ 2016

Asymptomatic Progressive Multifocal Leukoencephalopathy Associated with Natalizumab: Diagnostic Precision with MR Imaging[1]

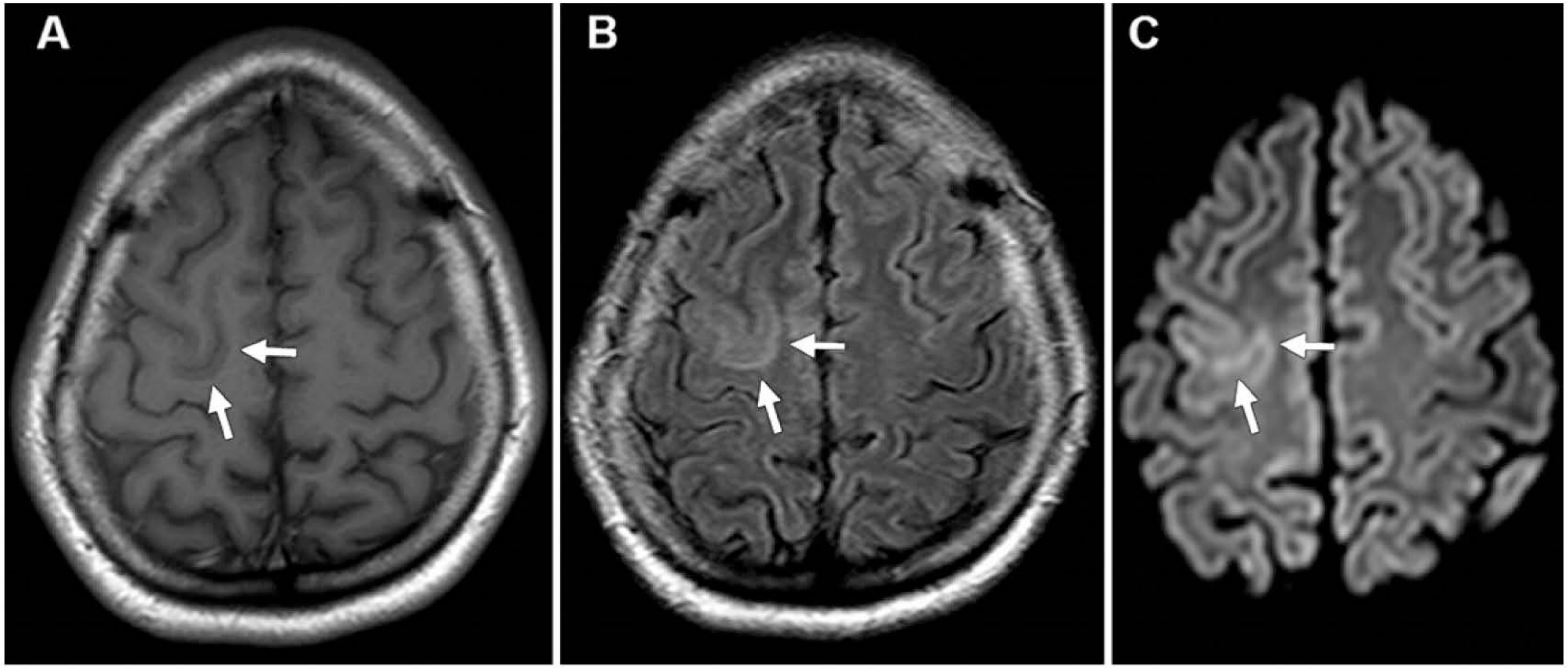


Figure 5: Axial MR images in 32-year-old patient with asymptomatic NTZ PML involving right precentral sulcus. *A*, NTZ PML lesion is confined in U fibers, slightly hypointense on T1-weighted image (arrows) and hyperintense on, *B*, FLAIR and, *C*, DW images (arrows).

Asymptomatic Progressive Multifocal Leukoencephalopathy Associated with Natalizumab:
Diagnostic Precision with MR Imaging[1]

Radiology: Volume 000: Number 0—■ ■ ■ 2016

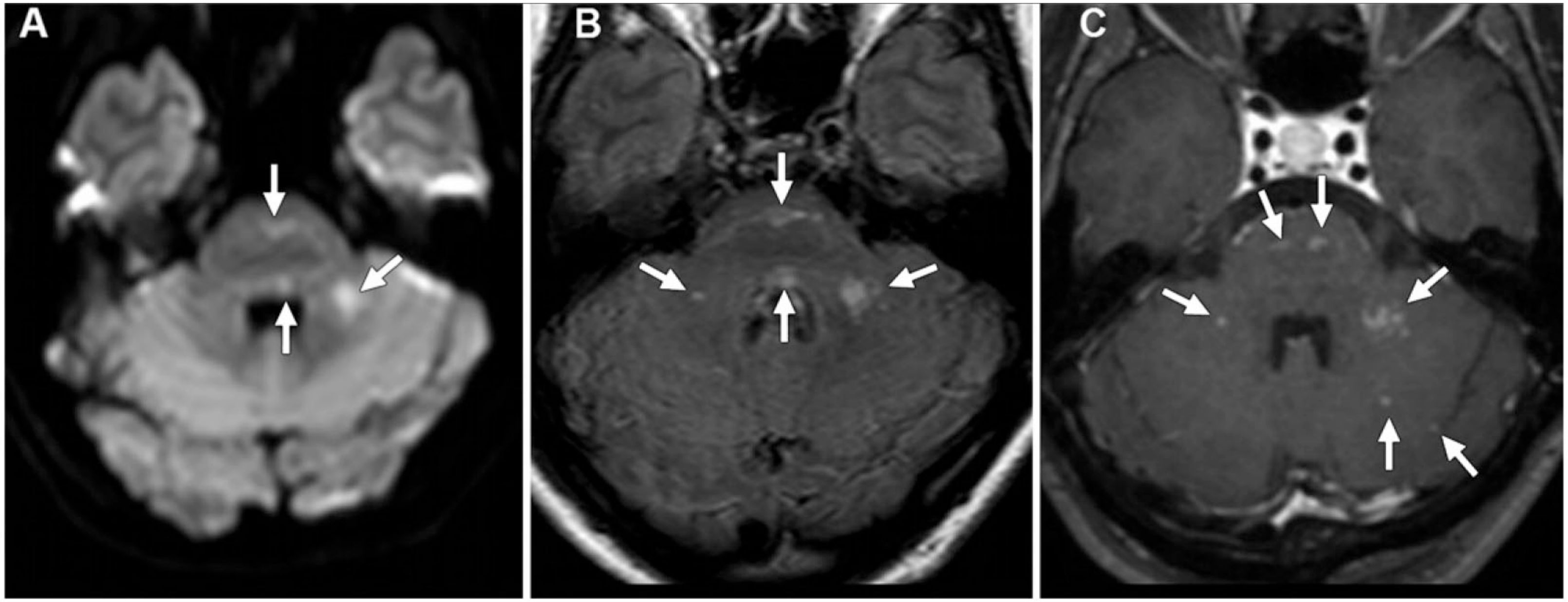


Figure 6: Axial MR images in 28-year-old patient with asymptomatic NTZ PML involving left middle cerebellar peduncle and brainstem. Hyperintense punctate lesions are visible on both, *A*, DW and, *B*, FLAIR images (arrows). *C*, On T1-weighted postcontrast image, additional enhanced punctate lesions are detected in cerebellum and brainstem (arrows).

Asymptomatic Progressive Multifocal Leukoencephalopathy Associated with Natalizumab: Diagnostic Precision with MR Imaging[1]

Radiology: Volume 000: Number 0—■ ■ ■ 2016

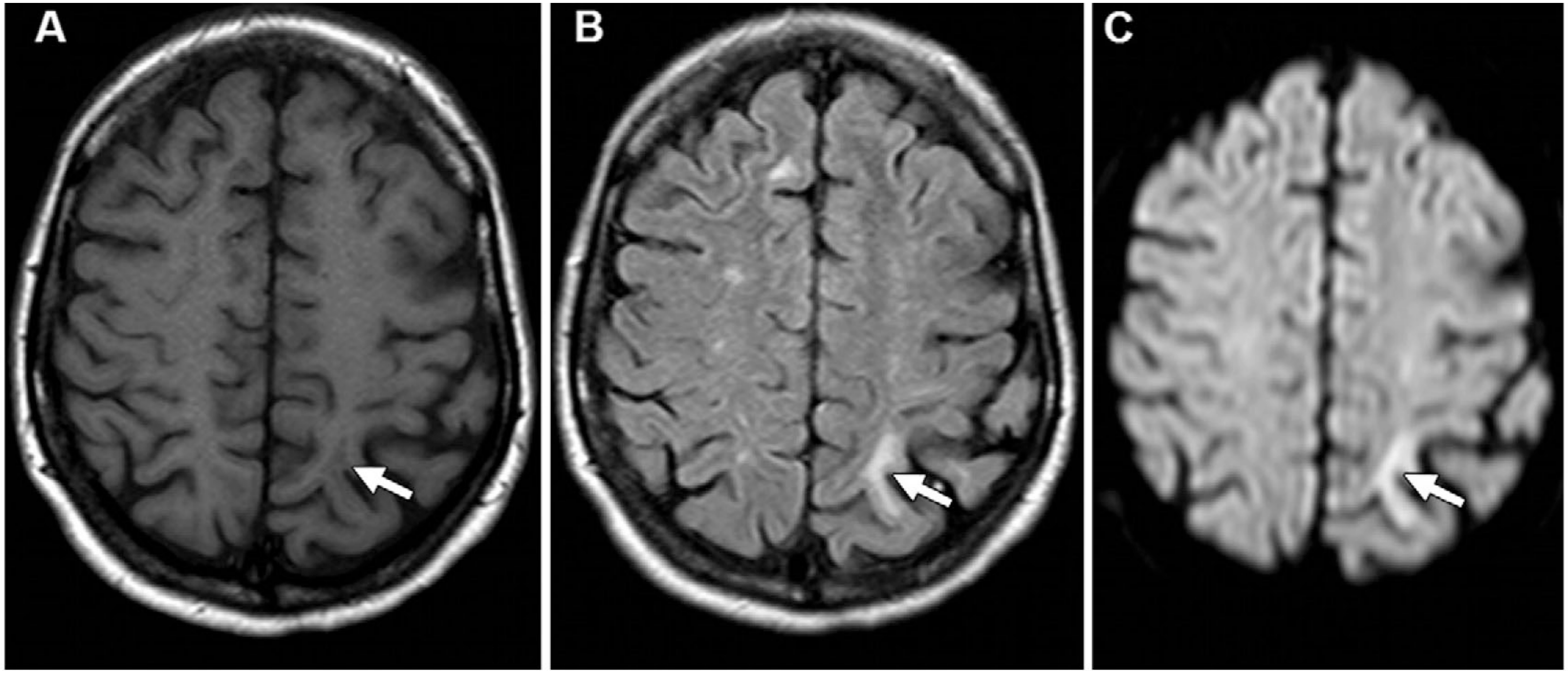
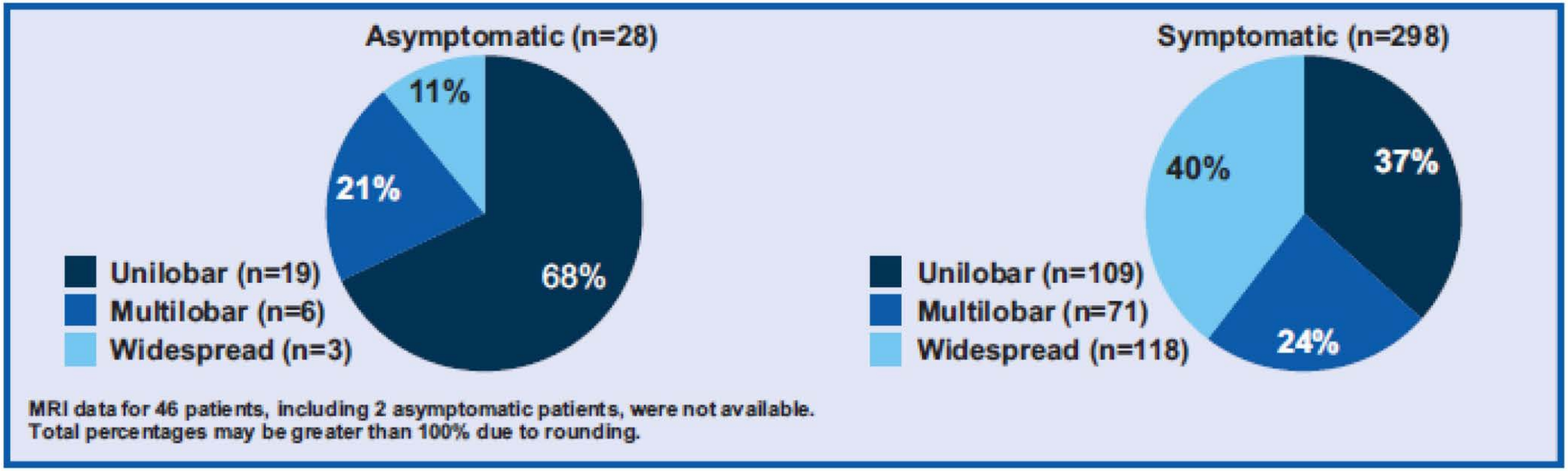


Figure 3: Axial MR images in 38-year-old patient with asymptomatic unilobar NTZ PML involving left parietal lobe. *A*, NTZ PML lesion involves U fibers and appears slightly hypointense on T1-weighted image (arrow) and hyperintense on, *B*, FLAIR and, *C*, DW images (arrows). Involvement of U fibers associated with hyperintensity on DW images was highly predictive of NTZ PML in this study.

MRG Bulguları

Asemptomatik PML'de lezyonların çoğu tek lobda bulunmaktadır.



- The majority of unilobar lesions in both groups of PML patients were in the frontal lobe
  - 71% (12/17) of asymptomatic
  - 52% (56/107) of symptomatic

Based on 372 natalizumab-PML cases confirmed as of June 5, 2013.
MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.
Dong-Si T et al. *Annals of Clinical and Translational Neurology.* 2014. [in press]

PML – Tedavi

PML Tedavisi

- Hastanın nörolojik açıdan yakın izlemi (duygu durum-bilişsel değerlendirme-görme alanı- nöbet varlığı)
- Hasta yakınlarının katkısının alınması
- MRG lerin aynı merkezde ve aynı sekans içeriklerinde ve kontrastlı çekilmesi
- MRG lerde spinal korda yer verilmesi
- Tıpkı nörolojik muayeneler gibi MRG ler arasında da karşılaştırma yapılması

PML Tedavisi

- PML nedeni olan ilacın kesilmesi
- Plazmaferez uygulanması
- ‘Wash-out’ sürecinin tamamlanmasından sonra da hastanın izlenmesi
- NM ve Manyetik rezonans görüntüleme ile izlem

PML Tedavisi

- 6 ayda bir JCV Ab değerlendirilmesi
- En uzun aralıklarla 12 ayda bir MRG yapılması (JCV Ab negatif hastalar da dahil olmak üzere)
- Kullanım süresi uzadıkça kar- zarar durumunun sürekli gözden geçirilmesi
- İndeksi > 1.5 olan hastalarda , >18 ayda, MRG sıklığının artırılması

PML Tedavisi

Sınıf	İlaç ismi	Mekanizma	Preklinik data	Klinik deneyim
Antiviral ajanlar				
JCV'nin hücreye girişini inhibe edenler	Chlorpromazine	Serotonin reseptör blokörü	Glial dokuda JCV'nin infeksiyon ve replikasyonunu inhibe eder.	Yok
	Citalopram Mirtazapine		JCV'nin 5HT2AR aracılığı ile girişini bloke eder.	Yok 4 olgu raporu (+)
	Risperidone		İn vitro olarak JCV'nin glial hücrelerdeki infeksiyonunu engelleyememektedir.	1 olgu sunumu (+)
	Ziprasidone			1 olgu sunumu (-)
Retrograd transport inhibitörleri	Retro-2cycl	Poliyoma virüslerin endoplazmik retikuluma taşınmasını retrograd olarak inhibe eder.	Kültür hücrelerinde infeksiyon başlamasını ve yayılmasını inhibe eder.	Yok
	Brefeldin A	Arf1 GTPase inhibitörüdür. Virüslerin endoplazmik retikuluma taşınmasını retrograd olarak inhibe eder.		

Pavlovic D, et al. Ther Adv Neurol Disord 2015;8(6):255-273

PML Tedavisi

Sınıf	İlaç ismi	Mekanizma	Preklinik data	Klinik deneyim
Antiviral ajanlar				
DNA replikasyon inhibitörleri	Cidofovir	Kendisi viral DNA'ya girerek viral replikasyonu inhibe eder, viral DNA polimerazı inhibe eder.	JCV için data yoktur. BK poliyomavirüs infeksiyonunu inhibe eder.	Klinik çalışmada yararlılık yok.
	Brincidofovir	Cidofovir'in derivatifidir.	İnsan beyin hücrelerinde JCV virüs replikasyonunu inhibe eder.	1 olgu sunumu (+), klinik çalışmada BK virüs enfeksiyonunda bulguları azaltma etkisi
	Cytarabine	Hem DNA hem de RNA polimerazı inhibe eder. Nükleotid redüktaz enzimini inhibe eder.	İn vitro olarak JCV replikasyonunu inhibe eder.	Klinik çalışmada yararlılık yok.
	Ganciclovir	Viral DNA polimerazı inhibe eder.	İnsan fibroblastlarında CMV ve JCV ortak replikasyonunu inhibe ettiği gösterilmiştir.	1 olgu sunumu (+)
	Leflunomide	DNA ve RNA sentezini inhibe eder.	BK ve JCV'nin in vitro inhibisyonu gösterilmiştir.	1 olgu sunumu (+)
	Topotecan	DNA replikasyonu sırasında DNA kırıkları oluşturarak DNA replikasyonunu inhibe eder.	İnsan glioblastom hücrelerinde JCV DNA'nın replikasyonunu baskılamıştır.	PML bireylerinde yapılan klinik çalışma fikir verici değildir.

Pavlovic D, et al. Ther Adv Neurol Disord 2015;8(6):255-273

PML Tedavisi

Sınıf	İlaç ismi	Mekanizma	Preklinik data	Klinik deneyim
Antiviral ajanlar				
Anti-malaryaller	Mefloquine	Bilinmiyor.	Kültür hücrelerinde JCV infeksiyon ve replikasyonunu inhibe eder.	Klinik çalışma yararlılık olmadığı için iptal edilmiştir.
PARP inhibitörleri	3-AB (3-amino-benzamide)	DNA onarımını engelleyerek DNA replikasyonunu inhibe ederler.	Nöroblastom hücre dizilerinde JCV'nin replikasyonunu in vitro olarak baskılarlar.	Yok
Tirozin kinaz inhibitörleri	Inhibikase IkT-001Pro (imatinib)	JCV infeksiyonunda mekanizma bilinmiyor	Yok	Yok
siRNA	Ag122	siRNA'e karşılık JCV agnoprotein	JCV enfekte hücre sayısı anlamlı olarak azaltmaktadır.	Yok
İmmün yanıt modülatörleri				
Sitokinler	IFN-alfa, IL-2, IL-7	Doğal ve kazanılmış bağışıklığın stimülasyonu	Yok	Olgu sunumu düzeyinde (+)
İnflamasyon inhibitörleri	Maraviroc	CCR5 aracılı doku inflamasyonunu bloke eder.	Yok	1 olgu sunumu (+)
	Glukokortikoidler	Genel immün sistem supresyonu	Yok	1 olgu sunumu (+)

Pavlovic D, et al. Ther Adv Neurol Disord 2015;8(6):255-273

PML Tedavisi

Sınıf	İlaç ismi	Mekanizma	Preklinik data	Klinik deneyim
İmmünizasyon				
Pasif immünizasyon	Rekombinan insan anti-JCV VP-1 monoklonal antikorları	JCV'nin nötralizasyonu	JCV nötralizasyonu ve özel bir hücre grubunun enfekte olmasının engellenmesi	Yok
	JCV-spesifik sitotoksik T lenfosit tedavisi	JCV enfekte hücrelerin lizisi	Yok	Olgu sunum (+)
Aktif immünizasyon	IL-7 + JCV VP1 aşısı	Yok	Yok	2 olgu sunumu (+)
	JCV oral aşısı	İnsan bağırsağında JCV spesifik immün yanıtın tetiklenmesi	Yok	Yok

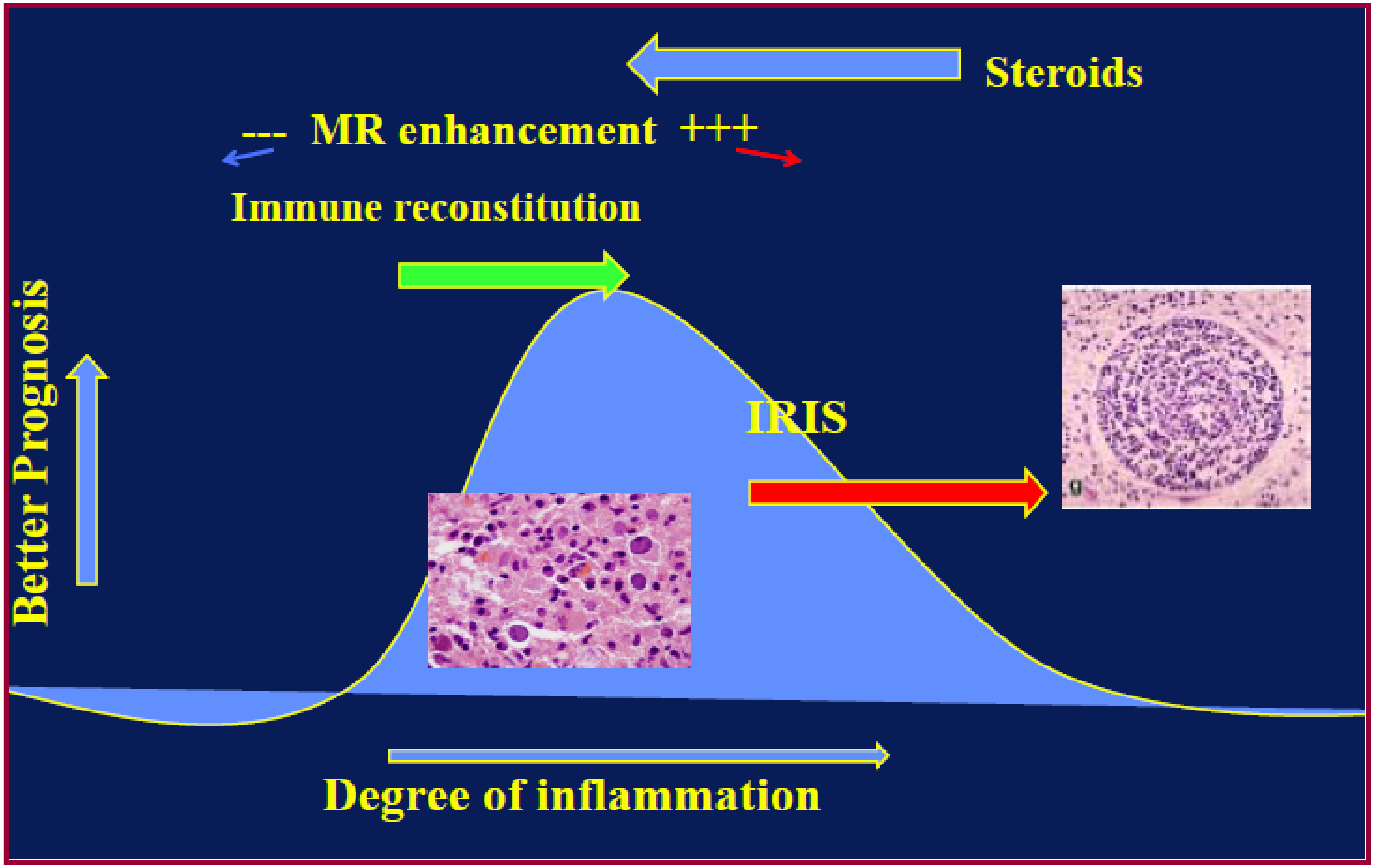
Pavlovic D, et al. Ther Adv Neurol Disord 2015;8(6):255-273

PML – IRIS
(Immune Reconstitution Inflammatory Syndrome)

PML-IRIS

- HAART ile HIV virus yükünde azalma
- CD4+ T lenfositlerde artış
- Klinikte paradoksal kötüleşme
- IRIS: CD8+ lenfositler, makrofajlar ile PML alanına infiltrasyon
- Az sayıda CD20+

PML-IRIS



Steroids
--- MR enhancement +++
Immune reconstitution
Better Prognosis
IRIS
Degree of inflammation

PML-IRIS

IRIS

- Natalizumab kesilmesi sonrasında
- Günler-haftalar - ortalama 3 ay
- Yoğun lenfosit infiltrasyonu
  - CD8 ağırlıklı T h aktivasyonu
- Erken ve geç görülebilir
- Kliniği kötüleştirebilir
- Yüksek doz MP ile tedavi edilmeli

Natalizumab: PML-IRIS

- Natalizumab kesilmesi sonrası lezyonlar
  - IRIS
  - MS aktivasyonu

The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy

Multiple Sclerosis Journal
19(14) 1826–1840

Mike P Wattjes[1], Nancy D Richert[2], Joep Killestein[3], Marlieke de Vos[1], Esther Sanchez[1], Petur Snaebjornsson[4], Diego Cadavid[2] and Frederik Barkhof[1]

Figure 10. PML-IRIS.
Axial T2-weighted (top row) and gadolinium-enhanced T1-weighted MR images (bottom row) of an MS patient with natalizumab-associated PML. Compared with the baseline scan (November 7, 2008), PML lesions (closed-head arrows) occurred in the white matter of both frontal lobes with the typical microcystic aspect without any contrast enhancement (January 27, 2010). Some of the acute PML lesions showed a perivascular distribution pattern (open-head arrows). After plasma exchange, the patient presented with a clinical decline and developed new and progressive lesions with an inhomogeneous appearance as well as areas with diffuse demyelination suggestive of PML-IRIS (March 24, 2010). On the post-contrast images, multifocal areas with (perivascular) enhancement are visible (open-head arrows). In addition, a linear area in the frontal cortical gray matter with T1 high signal intensity can be observed (small closed-head arrow). This finding does not represent contrast enhancement but cortical laminar necrosis.
PML: progressive multifocal leukoencephalopathy; IRIS: immune reconstitution inflammatory syndrome; MR: magnetic resonance.

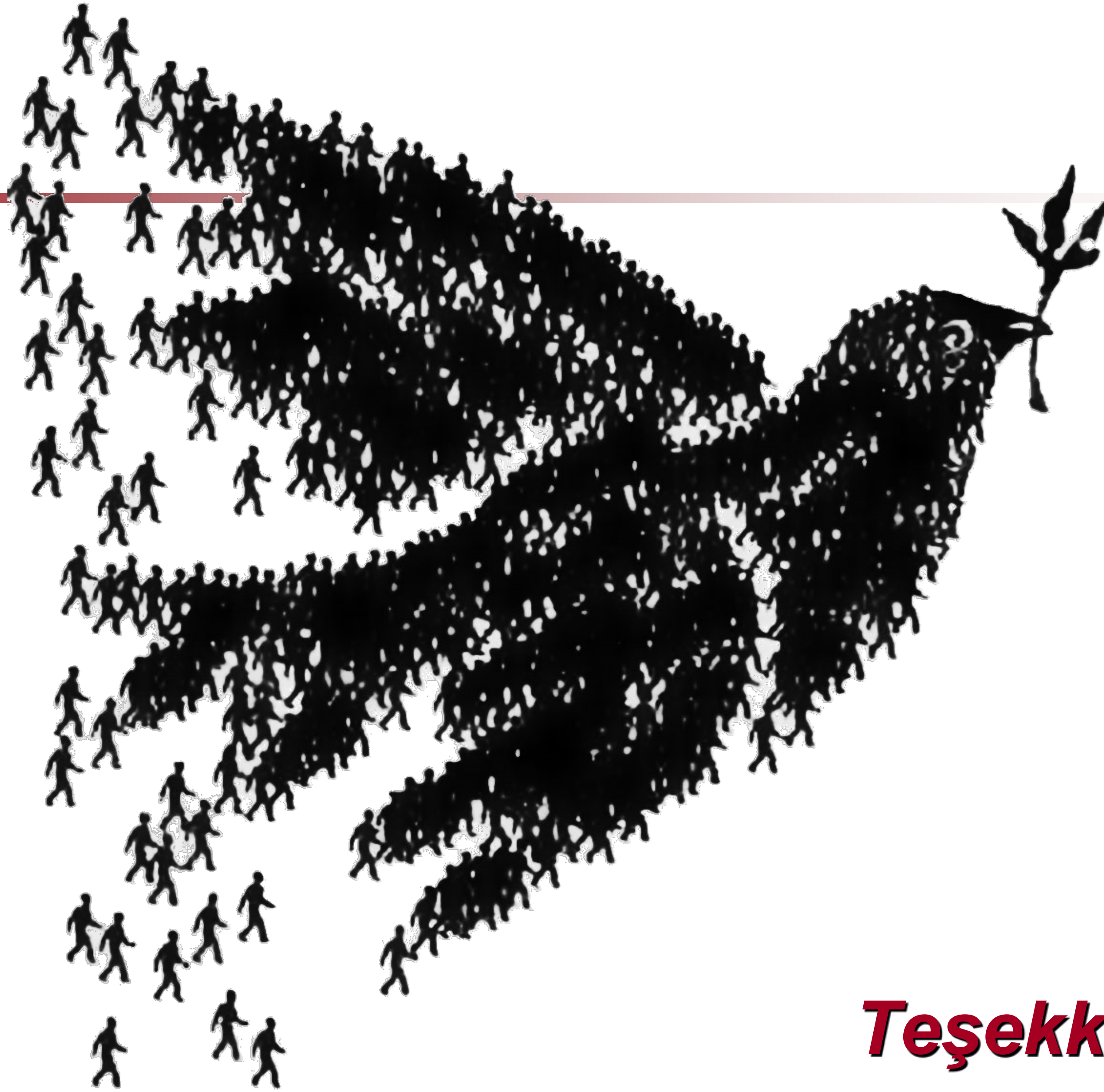
IRIS

- MS atağından ve olası fırsatçı enfeksiyonlardan ayrım yapılmalı
- İntravenöz metil prednizolon tedavisi 1000mg/gün, 3-5 gün, 3- 4 haftalık aralıklarla tekrarlanmalı
- Nörolojik muayene ve MRG bulgularına göre uzun süreli plan
- Maraviroc tedavisi (anti- CCR5)

Diğer Olası Durumlar

- Tüberküloz
- Hepatit B
- Herpes Virus Enfeksiyonları
- HIV
- Hepatit C


ANİD
ankara nöroimmünoloji derneği
9.
NÖROİMMÜNOLOJİ
OKULU
4 - 7 Nisan 2019
Hilton Dalaman Sarıgerme
Resort & Spa,
Muğla
flap tour
441. Cadde No: 1 Birlik, Çankaya / Ankara
Telefon: 0(312) 454 00 00
Faks:0 (312) 454 00 01
E-posta: noroimmunolojiokulu@flaptour.com.tr
www.noroimmunolojiokulu.org



Teşekkürler…