

Clinical Reasoning: A Teenager With Chronic Meningitis—Does Occam’s Razor Apply?

Harini Pavuluri, MD, DM, Vysakha KV, MD, DM, Bejoy Thomas, MD, George C. Vilanilam, MS, MCh, Prakash Nair, MS, MCh, Deepti A. Narasimhaiah, MD, Rajalakshmi Poyuran, MD, and Ramshekhar N. Menon, MD, DM

Correspondence
Dr. Menon
rsnmenon@yahoo.com

Neurology® 2023;100:828-835. doi:10.1212/WNL.0000000000206783

Abstract

A 14-year-old girl presented with subacute onset headache, fever, and vomiting and was managed initially with antibiotics for suspected bacterial meningitis. Her symptoms further evolved over the next few weeks with systemic signs and symptoms favoring chronic meningitis with raised intracranial pressure. After the etiologic workup was unrevealing, she was started on empirical antituberculous therapy. After a period of partial improvement, symptoms recurred with a new-onset focal seizure. Her imaging findings evolved from features suggestive of focal leptomeningitis to multifocal heterogeneous enhancing cortical and subcortical lesions with hemorrhagic foci, leading to brain biopsy that confirmed diagnosis. Our case highlights the utility of diagnostic biopsy in patients with “chronic meningitis” in uncertain cases rather than confining the approach to the law of parsimony. The decision to initiate empirical therapy in chronic meningitis should be considered on a case-by-case basis and take into account factors, such as clinical examination findings, immune status, recent exposures, and potential risks of treatment. Atypical MRI features should lower the threshold for meningocortical biopsy when indicated.

From the Department of Neurology (H.P., V.K.V., R.N.M.), Department of Imaging Sciences & Interventional Radiology (B.T.), Department of Neurosurgery (G.C.V., P.N.), and Department of Pathology (D.A.N., R.P.), Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 1

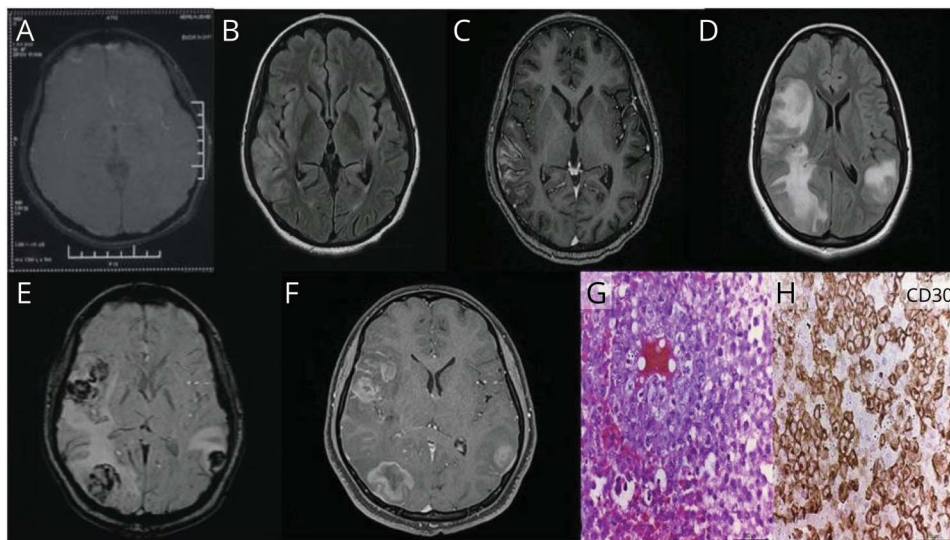
A 14-year-old girl presented with subacute onset, moderate intensity, progressive holocranial headache with photophobia, neck pain, and recurrent episodes of vomiting, followed by low-grade fever and myalgias 4 days later. Ten days into the illness she was admitted to a local hospital after she did not improve with analgesics and antipyretics. She then underwent MRI which showed patchy, linear, and subtle leptomeningeal enhancement suggestive of meningitis (Figure, A) and CSF analysis which showed hypoglycorrhachia, elevated protein, and lymphocytic pleocytosis. She was managed with empirical ceftriaxone and vancomycin for 10 days for presumed bacterial meningitis. She subsequently developed intermittent binocular horizontal diplopia with recurrence of intermittent headache and fever. She was referred to our center 45 days into the illness. On admission, her general examination was unremarkable. Neurologic examination showed right abducens palsy and positive Kernig and Brudzinski signs, with no other

deficits. After a repeat MRI brain (Figure, B and C), lumbar puncture, and extensive investigations, she was started on antituberculous therapy (ATT) with steroids. There was marked improvement initially; however, on attempted steroid taper after 4 months, she suffered recurrence of headache and 1 episode of focal-onset seizure with impaired awareness. Repeat examination did not reveal any features of raised intracranial pressure (ICP) or focal neurologic deficits. MRI after clinical relapse showed multiple heterogeneous T2/fluid-attenuated inversion recovery (FLAIR) hyperintense cortical and subcortical lesions with multiple microhemorrhages on susceptibility-weighted imaging and patchy enhancement (Figure, D and F), without diffusion restriction and normal MR spectroscopy and perfusion.

Question for Consideration:

1. What is the clinical approach to this patient with headache, and what etiologic possibilities should be considered?

Figure Serial MRI and Final Histopathology Images



(A) Subtle leptomeningeal enhancement noted 3 weeks into illness. (B) FLAIR hyperintensity in the right parietotemporal lobe. (C) Patchy enhancement of the hyperintense region on a T1W contrast sequence noted at 6 weeks suggestive of progression. (D) Multiple heterogeneous T2/FLAIR hyperintense cortical and subcortical lesions at the grey-white matter junction of the right frontotemporal, parieto-occipital, and left temporal lobe. (E) Multiple foci of blooming on SWI and heterogeneous enhancement of the hyperintense lesions. (F) Leptomeningeal enhancement on T1W contrast at 6 months. (G) Histopathology images showing atypical large lymphoid cells with vesicular nuclei and prominent nucleoli and brisk mitotic activity on hematoxylin and eosin staining. (H) CD30-positive atypical lymphoid cells on immunoperoxidase staining (magnification = scale bar G, H: 50 μ m). FLAIR = fluid-attenuated inversion recovery; T1W = T1-weighted; T2W = T2-weighted.

GO TO SECTION 2

Section 2

This patient presented with fever and subacute progressive headache with associated vomiting, photophobia, and neck pain. Given the potential origin of pain from the meninges, proximal arteries of the circle of Willis, meningeal arteries, or dural venous sinuses,^{1,2} potential etiologies included pachymeningitis (from infectious causes or inflammatory etiologies including sarcoidosis, immunoglobulin G4-mediated disease, and neoplastic processes), primary or secondary CNS angiitis, and cerebral venous thrombosis with or without intracranial hypertension. Although primary headache disorders, such as migraine and trigeminal autonomic cephalalgias, are also possibilities, her progressive course and abnormal CSF profile made

these conditions less likely. Secondary headache was suspected in view of neck pain, rigidity, recurrent vomiting, diplopia with fever, and myalgias.^{2,3} Later in the disease course, development of focal-onset seizures may also indicate an evolving encephalitis or space-occupying lesion of probable infectious (bacterial, fungal, tubercular, or cysticercosis), inflammatory (sarcoidosis, Behcet disease, Wegener granulomatosis, or nongranulomatous connective tissues disorders with angiitis such as systemic lupus erythematosus, polyarteritis nodosa, Vogt Koyanagi Harada, or primary CNS angiitis), or neoplastic etiologies (leukemia or lymphoma, given the patient's age).⁴

Question for Consideration:

1. What are the investigative approaches?

GO TO SECTION 3

Section 3

Imaging and CSF analysis are 2 seminal diagnostic modalities that should be considered in any patient presenting with a new-onset secondary headache with or without fever, which often guide further diagnostic workup. Brain imaging should be undertaken before lumbar puncture in cases of headache/raised ICP to reduce the risk of herniation. Serial CSF analysis (Table 1) from time of symptom onset showed a persistent lymphocytic pleocytosis with hypoglycorrhachia and elevated

protein. Other investigations and serial MRI findings are summarized, respectively, in Table 1 and the Figure. The CSF findings of elevated protein and low glucose with pleocytosis which persisted for more than 6–8 weeks raised concern for chronic meningitis. The differential diagnosis is discussed in Table 2.^{4,5}

Question for Consideration:

1. How do you interpret the imaging findings in this patient?

Table 1 Summary of Serial CSF Findings and Other Ancillary Investigations

Serial CSF analysis findings					
Lumbar puncture (date)	I (October 26, 2017)	II (October 30, 2017)	III (November 20, 2017)	IV (December 5, 2017)	V (April 19, 2018)
Total cell count (cells/mm ³)	120	120	98	35	20
Differential cell count (N: neutrophils; L: lymphocytes in %)	N 2, L 98; no dysplastic cells	N 8, L 92; no dysplastic cells	N 20, L 80	N 2, L 98	N 20, L 80
Malignant cell cytology	Negative	Negative	Negative	Negative	Negative
Glucose (corresponding blood glucose; mg/dL)	31 (170)	49 (182)	28 (120)	46 (117)	46 (95)
Protein (mg/dL)	131	164	215	84	114
Culture (bacterial, fungal and viral)	Negative	Negative	Negative	Negative	Negative
PCR meningitis/encephalitis panel				Negative	Negative
Cryptococcal antigen and pan fungal assay				Negative	Negative
Gene Xpert for mycobacterium				Negative	Negative

Other investigations

Hemogram, liver function tests, renal function tests, thyroid function tests: normal
 CRP, ESR, procalcitonin: normal
 Vasculitis profile (ANA, anti-ds DNA, ANCA, APLA) and ANA profile: negative
 Brucella serology: negative
 Viral markers (HIV, HBsAg, anti HCV): negative
 Serum tumor markers: negative
 Serum calcium profile and ACE level: normal
 CT chest and abdomen contrast enhanced, DSA: normal

Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; APLA = antiphospholipid antibody; CRP = C-reactive protein; DSA = digital subtraction angiography; ESR = erythrocyte sedimentation rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis B virus.

Table 2 Differential Diagnosis for Chronic Meningitis With Significant Hypoglycorrhachia and Lymphocyte-Dominant Pleocytosis

Infective causes	Noninfectious inflammatory causes	Neoplastic
<p>Bacterial</p> <ul style="list-style-type: none"> • Partially treated bacterial meningitis • Mycobacterium tuberculosis and atypical mycobacterial infections • Borreliosis • Nocardiosis • Brucellosis • Melioidosis • Syphilis <p>Fungal</p> <ul style="list-style-type: none"> • Cryptococcosis • Histoplasmosis • Coccidioides • Candidiasis • Aspergillosis • Phaeohyphomycosis <p>Parasitic</p> <ul style="list-style-type: none"> • Acanthamoeba • Balamuthia • Toxoplasmosis • Cysticercosis <p>Viral</p> <ul style="list-style-type: none"> • HIV • Herpes simplex 1 and 2 • Lymphocytic choriomeningitis virus 	<ul style="list-style-type: none"> • Sarcoidosis • Neuro-Behcet's disease 	<ul style="list-style-type: none"> • Leukemia • Lymphoma (late relapse after steroid taper) • Leptomeningeal metastasis

The differentials to be considered in the setting of a CSF profile with significant hypoglycorrhachia and lymphocyte dominant pleocytosis.⁴⁻⁶

GO TO SECTION 4

Section 4

Infections usually produce a thin, linear enhancement (Figure, A) except for fungal meningitis and tuberculosis which cause thick, lumpy, and nodular enhancement patterns. In addition, enhancement due to a neoplastic process is usually thick, lumpy, and nodular; however, carcinomatous meningitis and hematological malignancies, such as lymphoma and leukemia, can produce a thin linear enhancement pattern when compared to solid tumors.⁷ Presence of a cortical gyriiform FLAIR hyperintensity with enhancement (Figure, B and C) was suggestive of a cortical laminar necrosis, either after a vascular insult or focal encephalitis.⁷ These important vascular

conditions include subacute infarcts, posterior reversible encephalopathy syndrome, and postictal vasodilatation. Inflammatory causes can include either infectious (e.g., herpes simplex virus encephalitis) or noninfectious autoimmune disorders, with neoplasms being rare mimics.⁷ MRI after clinical relapse (Figure, D and F) suggested a vasculitic process or systemic neoplasm, such as Hodgkin or non-Hodgkin lymphoma (NHL).⁸

Question for Consideration:

1. What differential should be considered in light of the clinical and investigative imaging and CSF findings, and how do you proceed further?

GO TO SECTION 5

Section 5

Progressive worsening of clinical and radiographic findings with persistent CSF abnormalities, despite a 4-drug ATT regimen and steroid coverage, prompted further etiologic exploration. The final possibilities that should be considered include:

1. Infectious meningitis with secondary CNS vasculitis: presence of fever at symptom onset and hypoglycorrhachia with lymphocytic pleocytosis raised concern for infection (fungal, tubercular, and parasitic). However, molecular diagnostics were negative for most infections, and this patient was young and immunocompetent without history or exposure to tuberculosis. Although immune reconstitution inflammatory syndrome⁹ is still possible, atypical imaging features with microhemorrhages were less suggestive. Digital subtraction angiography for vasculitis was also unremarkable.
2. Multicentric high-grade glioma or CNS lymphoma: normal perfusion and spectroscopy make glioma less likely. Although CNS lymphoma is a strong possibility, atypical imaging features included extensive microhemorrhages, heterogeneous enhancement, peripheral location, and absence of diffusion restriction. The use of corticosteroids may also have mitigated these imaging findings.

As most investigations had been unrevealing, she underwent a neuronavigation-guided biopsy 6 months into the illness of an enhancing lesion in the right temporal lobe. Twenty-four hours after the biopsy, she required a decompressive craniectomy with uncinctomy and right temporal lobectomy after she developed encephalopathy with features of intracranial hypertension and CT demonstration of midline shift. Biopsy was suggestive of anaplastic large cell lymphoma (ALCL), a rare T-cell NHL variant (Figure, G and H).

A whole body 18F-fluoro-deoxy-glucose PET performed subsequently showed multiple foci of hypermetabolism in muscles and body of the pancreas. She received 7 cycles of chemotherapy with high-dose methotrexate, vincristine, procarbazine, and dexamethasone and whole brain irradiation at a dose of 45 Gray in 25 fractions with excellent response and achieved complete remission. Repeat PET and MRI showed no residual lesion or recurrence. No neurologic or cognitive deficits were apparent on her last clinical evaluation.

Discussion

Primary and secondary CNS lymphomas are a rare subset of NHL especially in the pediatric age group.^{10,11} Primary CNS lymphoma is confined to the CNS parenchyma, meninges, cranial nerves, spinal cord, or intraocular compartment, while secondary CNS lymphoma results from systemic NHL that has disseminated to the CNS with a predilection for the dura and leptomeninges.¹² ALCL is a rare T-cell NHL which frequently involves lymph nodes and extranodal sites, such as the bone marrow, liver, or gastrointestinal tract, and rarely involves the

CNS. Less than 50 cases of CNS ALCL have been reported.¹³ ALCL has predilection for young adults (median age at onset 21 years) and is divided into anaplastic lymphoma kinase (ALK)-positive and ALK-negative subtypes based on ALK expression. Our patient had systemic ALCL with cerebral involvement and ALK-positive status (cytoplasmic and membrane).

Most cases present with meningeal involvement, suggestive of a dural origin of the tumor and can be misdiagnosed initially as chronic infectious causes of inflammatory meningitis, stemming from a fungal infection, tuberculosis, or sarcoidosis.¹³ In a recent systematic review of 36 cases, one-third of patients received initial empirical treatment with antibiotics, antituberculous, and antiviral medications akin to our case.¹³ Multiple lesions with meningeal involvement on imaging are common; however, the presence of extensive microhemorrhages with perilesional edema is unique to our case. Diagnostic biopsy followed by methotrexate-based chemotherapy with or without radiotherapy is the recommended line of management. Younger age at onset, ALK-positive status, and methotrexate-based chemotherapy are favorable prognostic factors,¹³ also highlighted in our case.

This report underscores the clinic-radiologic and pathologic heterogeneity of ALCL with potential therapeutic and prognostic implications in a teenager suspected to have an infectious etiology for her chronic meningitis. The utility of diagnostic biopsy in patients with “chronic meningitis” is also emphasized in uncertain cases, rather than remaining confined to the concept of Occam’s razor (law of parsimony). This approach is error-prone because the principle encourages us not to seek multiple diagnostic possibilities beyond what is most likely after clinical examination, imaging, and CSF analysis.¹⁴ The decision to initiate empirical therapy with antibiotics or ATT and steroids (often driven by epidemiologic considerations) in chronic meningitis should be considered on a case-by-case basis. This approach should also take into account the overall picture and potential risks of treatment that can lead to diagnostic delays and clinical deterioration. The use of empirical steroids can cause transient improvement but can decisively alter the clinical, CSF, radiologic, and histopathologic findings in cases of CNS lymphoma as highlighted in our report. In such situations, a lower threshold for biopsy is warranted.

Study Funding

No targeted funding reported.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* May 28, 2022. Accepted in final form November 21, 2022. Submitted and externally peer reviewed. The handling editor was Resident & Fellow Section Editor Whitley Aamodt, MD, MPH.

Appendix Authors

Name	Location	Contribution
Harini Pavuluri, MD, DM	Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Vysakha K.V., MD, DM	Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Bejoy Thomas, MD	Department of Imaging Sciences & Interventional Radiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
George C. Vilanilam, MS, MCh	Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Prakash Nair, MS, MCh	Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Deepti A. Narasimhaiah, MD	Department of Pathology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Rajalakshmi Poyuran, MD	Department of Pathology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Ramshekhar N. Menon, MD, DM	Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Kapoor S. Headache attributed to cranial or cervical vascular disorders. *Curr Pain Headache Rep.* 2013;17(5):334. doi:10.1007/s11916-013-0334-y.
2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018; 38(1):1-211. doi:10.1177/0333102417738202.
3. Jankovic J, Mazziotto JC, Pomeroy SL, Newman NJ, editors. *Bradley and Daroff's Neurology in Clinical Practice.* Philadelphia: Elsevier; 2022.
4. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine, 20th ed. (Vol. 1 & Vol. 2).* McGraw-Hill Education. 2018.
5. Aksamit AJ. Chronic meningitis. *N Engl J Med.* 2021;385(10):930-936. doi:10.1056/NEJMr2032996.
6. Baldwin KJ, Zunt JR. Evaluation and treatment of chronic meningitis. *Neurohospitalist.* 2014;4(4):185-195. doi:10.1177/1941874414528940.
7. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *RadioGraphics.* 2007;27(2):525-551. doi:10.1148/rg.272065155.
8. Hajji-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angitis of the CNS. *Lancet Neurol.* 2011;10(6):561-572. doi:10.1016/S1474-4422(11)70081-3.
9. Jagannathan D, Chakkalakkoombil SV, Beena AA, Krishnan N. Neurotuberculosis immune reconstitution inflammatory syndrome in the setting of HIV infection: a case report and review of literature. *Indian J Radiol Imaging.* 2016;26(04):446-450. doi:10.4103/0971-3026.195782.
10. Grommes C, Rubenstein JL, DeAngelis LM, Ferreri AJM, Batchelor TT. Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. *Neuro-Oncol.* 2019;21(3):296-305. doi:10.1093/neuonc/ny192.
11. Attarbaschi A, Abal O, Ronceray L, et al. Primary central nervous system lymphoma: initial features, outcome, and late effects in 75 children and adolescents. *Blood Adv.* 2019;3(24):4291-4297. doi:10.1182/bloodadvances.2019001062.
12. Abal O, Weitzman S, Blay JY, et al. Primary CNS lymphoma in children and adolescents: a descriptive analysis from the International Primary CNS Lymphoma Collaborative Group (IPCG). *Clin Cancer Res.* 2011;17(2):346-352. doi:10.1158/1078-0432.CCR-10-1161.
13. Hirano Y, Miyawaki S, Tanaka S, et al. Clinical features and prognostic factors for primary anaplastic large cell lymphoma of the central nervous system: a systematic review. *Cancers.* 2021;13(17):4358. doi:10.3390/cancers13174358.
14. Schaffer J. What not to multiply without necessity. *Australas J Philos.* 2015;93(4):644-664.

Did You Know...

...you can browse by subspecialty topics on [Neurology.org](https://www.neurology.org)?

Go to: [Neurology.org](https://www.neurology.org) and click on "Collections" in the top navigation bar, then choose "Topics A-Z" from the drop down menu.

Neurology®

Clinical Reasoning: A Teenager With Chronic Meningitis—Does Occam's Razor Apply?

Harini Pavuluri, Vysakha KV, Bejoy Thomas, et al.

Neurology 2023;100;828-835 Published Online before print February 6, 2023

DOI 10.1212/WNL.0000000000206783

This information is current as of February 6, 2023

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/100/17/828.full
References	This article cites 12 articles, 1 of which you can access for free at: http://n.neurology.org/content/100/17/828.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Immunology http://n.neurology.org/cgi/collection/all_immunology All Oncology http://n.neurology.org/cgi/collection/all_oncology MRI http://n.neurology.org/cgi/collection/mri
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2023 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

