MRI of Toxic, Metabolic, and Autoimmune Encephalopathies: A Review

Jose Gavito-Higuera, MD; Carola Mullins, MD; Lisa Ivette Gutierrez-Villalobos, MD; Hugo Sandoval, PhD; Jason Shewchuk, MD; and Luis Ramos-Duran, MD

Encephalopathies encompass a wide range of etiologies, including intoxications, autoimmune disorders, and metabolic imbalances. Symptoms are often nonspecific and range from seizures, focal neurological deficits, and movement disorders, to coma, permanent sequelae and death.[1] MRI is the imaging modality of choice and is often the first indicator of an encephalopathy as a possible cause of symptoms.[1] Recognition of distinct MRI enhancement patterns in regard to symmetry and topographic distribution can help identify the underlying pathology.

This article highlights the vital role the radiologist plays in identifying these manifestations, which in some cases are reversible. We also illustrate the most common toxic, autoimmune, and metabolic encephalopathies to create an understanding and awareness of typical imaging appearances the radiologist may encounter (Table 1).

Dr. Gavito-Higuera, Dr. Gutierrez-Villalobos, and Dr. Ramos-Duran are Radiologists at the Texas Tech University Health Sciences Center, El Paso, TX. Dr. Mullins and Dr. Sandoval are Imaging Researchers at the Texas Tech University Health Sciences Center, El Paso, TX. Dr. Shewchuk is a Professor of Radiology at the University of British Columbia, Vancouver, BC. The authors have no conflicts of interest to disclose. *This article is based on a pictorial essay previously presented at RSNA 2016.*

Toxic Etiologies

Thermatrim Encephalopathy

Thermatrim, a thermogenic dietary supplement marketed to promote weight loss, has been associated with anxiety, insomnia, cardiovascular disorders, and central nervous stimulation.[2] Imaging findings are characteristic for extensive symmetric involvement of the corpus callosum, pons, and the subcortical white matter, with hyperintensities on T2-weighted imaging (T2-WI) and restricted diffusion on Diffusion Weighted Imaging (DWI) with reduced Apparent Diffusion Coefficient (ADC) values (Figure 1).[2]

Methanol Encephalopathy

The clinical presentation usually involves visual disturbances as a first symptom followed by headaches, dizziness, malaise, seizures, stupor, and coma after a latent period.[3] Intoxication can be fatal unless treated early and characteristically involves bilateral necrosis of the putamina with or without hemorrhage.[4] Variable signal intensities on T1-weighted imaging (T1-WI) with enhancement after contrast administration, hyperintensities on T2-WI, and Fluid Attenuation Inversion Recovery (FLAIR) sequences, and restricted diffusion on DWI, are typical imaging findings (Figure 2).[4]

Carbon Monoxide Encephalopathy

Carbon-monoxide intoxications may be accidental or intentional and present with nonspecific symptoms and signs ranging from headaches and confusion to coma and death.[4] Exposure can be acute or chronic, and bilateral symmetric necrosis of the globi pallidi with or without involvement of the caudate and putamina is characteristic.[4] Hypointensities on T1-WI and hypertintensities on T2-WI are distinct imaging findings and their extent correlates with clinical outcome (Figure 3).[4]

Heroin Encephalopathy

Heroin can be administered through multiple routes, including intravenous injection, oral use, and vapor inhalation, also referred to as "chasing the dragon." Leukoencephalopathy related to heroin vapor inhalation progresses from cerebellar signs and motor restlessness to pyramidal and pseudobulbar signs and eventually to spasms, paresis, and death.[5] Symmetric high signal intensity

Table 1. Acquired encephalopathic processes

Toxic	Autoimmune	Metabolic
Thermatrim	Anti-NMDA R-encephalopathy	Central Pontine Myelinolysis / Osmotic Demyelination
Heroin	Hashimoto	Wernicke Encephalopathy
Methanol	Limbic	Non-ketotic hyperglycemic hemichorea
Carbon-monoxide		Hypoxic
Tacrolimus		Hypoglycemic
		Hepatic
		Hyperammonemic

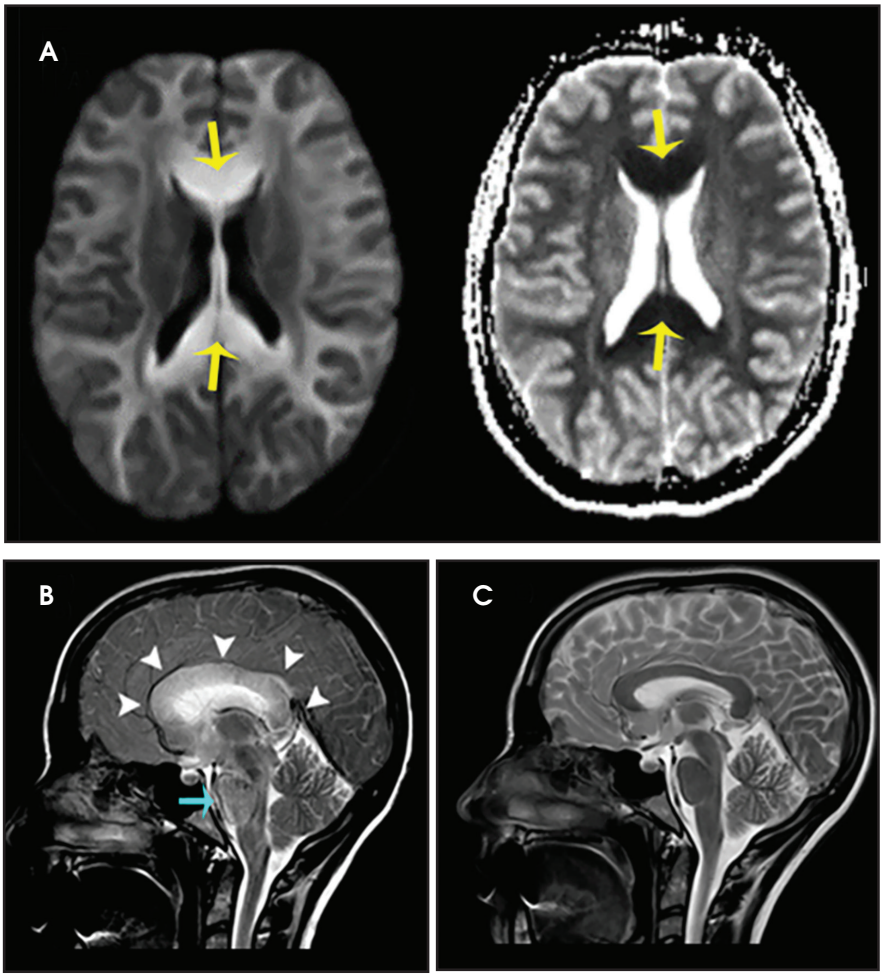

FIGURE 1. *A 19-year-old taking Thermatrim as a weight loss supplement presented with headaches and photophobia. (A) Axial DWI and ADC map demonstrate abnormal hyperintensity and corresponding restricted diffusion of the corpus callosum (yellow arrows). (B) Sagittal T2-WI demonstrates diffuse abnormal hyperintensity of the corpus callosum (white arrowheads) and of the pontine tegmentum (blue arrow). (C) Two-month follow-up sagittal T2-WI demonstrates near complete interval resolution of the hyperintensities of the corpus callosum and pons.*

on T2-WI MRI and FLAIR sequences with involvement of the cerebellum and posterior limbs of the internal capsules are characteristic (Figure 4).[5] Heroin encephalopathy is typically associated with ischemia, and 5-10% of all heroin users have infarcts of the globi pallidi.[6] High signal intensities in the subcortical and periventricular white matter on T2-WI are also characteristic imaging findings (Figure 4).[6]

Tacrolimus Encephalopathy

The calcineurin inhibitor tacrolimus is administered in the prophylaxis of graft-versus-host disease. About 40-60% of all treated patients suffer from headaches, paresthesia, tremor, and sleep disturbances, and 5-8% exhibit signs of confusion, lethargy, dysarthria, seizures, and coma.[7] Bilateral edema in the subcortical white matter is characteristic and corresponds to hyperintensities on T2-WI and FLAIR sequences (Figure 5).[7]

Autoimmune Etiologies

Hashimoto Encephalopathy

Hashimoto encephalopathy, associated with autoimmune disease involving the thyroid, can present either as neurological deficits or as progressive cognitive decline with dementia or psychosis.[8] Seizures are usually present in both forms, and anti-thyroid antibodies, in particular antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG), can be detected. Imaging findings are potentially reversible and are characteristic for bilateral symmetric involvement of the temporal lobes and basal ganglia, with diffuse increased signal intensities on T2-WI and FLAIR sequences (Figure 6).[8]

Anti-N-Methyl-D-Aspartate Receptor (NMDA R) – Encephalopathy

NMDA R-encephalopathy is associated with serum or cerebrospinal fluid autoantibodies against subunits of the NMDA receptor. Signs include auditory and visual hallucinations, behavior changes, impaired consciousness, seizures, movement disorders, and

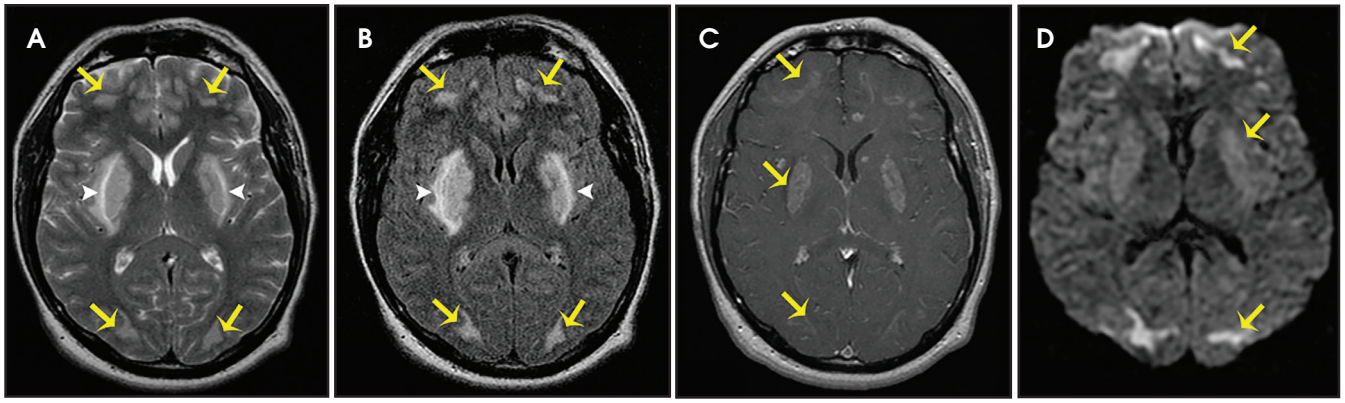

FIGURE 2. *A 30-year-old man was admitted to the hospital with headaches and altered mental status after methanol ingestion. (A) Axial T2-WI and (B) FLAIR demonstrate bilateral symmetric putaminal hyperintensities (white arrowheads) and bilateral hyperintense signal involving the frontal and occipital subcortical white matter (yellow arrows). (C) Axial MRI T1-WI postcontrast shows corresponding abnormal enhancement (yellow arrows). (D) DWI shows restricted diffusion predominantly in the frontal and occipital region (yellow arrows).*

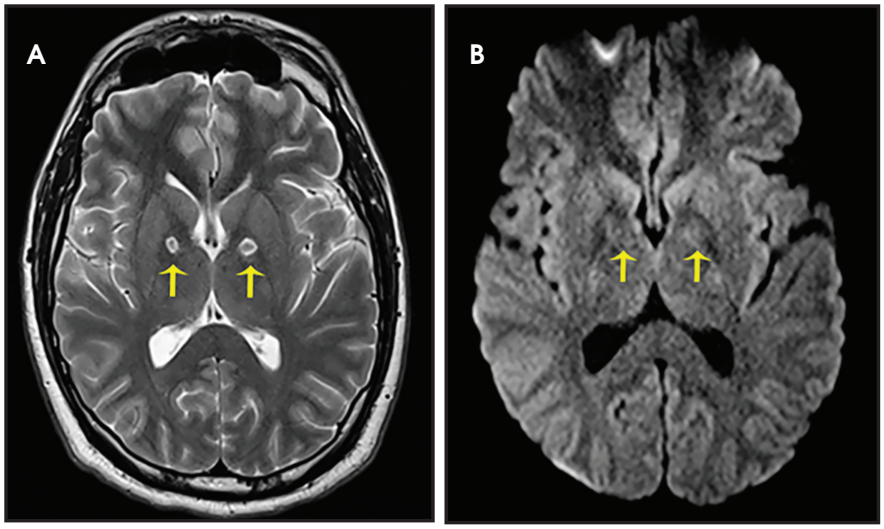

FIGURE 3. *A 40-year-old woman with carbon monoxide poisoning was found in a coma. (A) MRI T2-WI in axial view shows increased signal intensity of both globus pallidi in a symmetric fashion (yellow arrows). (B) Corresponding DWI shows no evidence restricted diffusion (yellow arrows).*

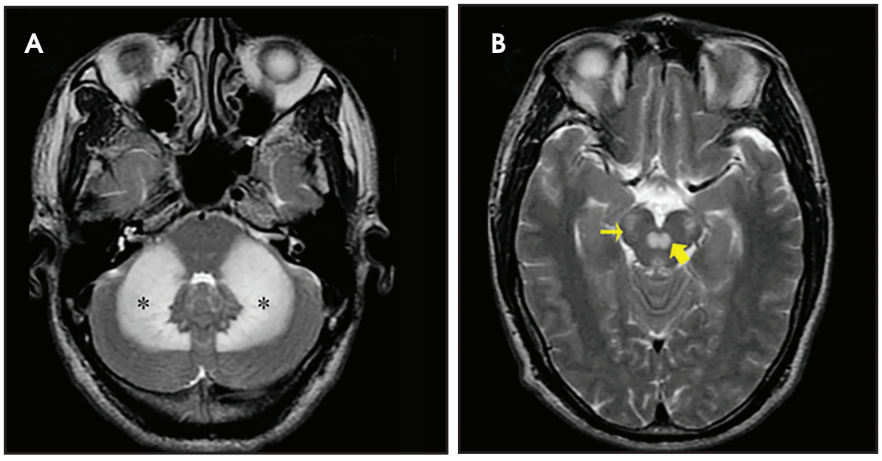

FIGURE 4. *40-year-old man with a history of heroin abuse and altered mental status. (A) Axial MRI T2-WI demonstrates bilateral hyperintensities of the middle cerebellar peduncles (black asterisks). (B) Axial MRI T2-WI shows hyperintensities of the red nuclei (thick yellow arrow) and cerebral peduncles (corticospinal tracts) (thin yellow arrow).*

autonomic dysfunction.[9] In 59% of cases, an ovarian tumor can be identified and the overall associated mortality is up to 25%.[9] Diagnostic imaging is often normal but may demonstrate hyperintensities of the hippocampi, cerebellar and cerebral cortex, basal ganglia, brainstem, fronto-basal, and insular regions, and should include appropriate studies to rule out an ovarian teratoma (Figure 7).[9]

Limbic Encephalitis (LE)

LE can be the paraneoplastic manifestation of an underlying, often undetected, malignancy associated with various antibodies against neuronal and tumor cells or it can be non-neoplastic, and in that case most commonly identifiable through the presence of voltage-gated, potassium channel antibodies (VGKG).[10] Onset is generally subacute with temporal lobe seizures, memory loss, and confusion. Temporomesial changes with uni- or bilateral swelling are visible on T2-WI and FLAIR sequences and may progress to atrophy (Figure 8).[10]

Metabolic Etiologies

Hypoxic Encephalopathy

Hypoxic encephalopathy occurs because of either hypoperfusion or hypoxia, and the duration of the insult, the degree of perfusion, temperature, and glucose levels determine the extent of the cerebral injury.[1]Structures of the gray matter, such as cerebral cortex, basal ganglia, or hippocampi, are usually

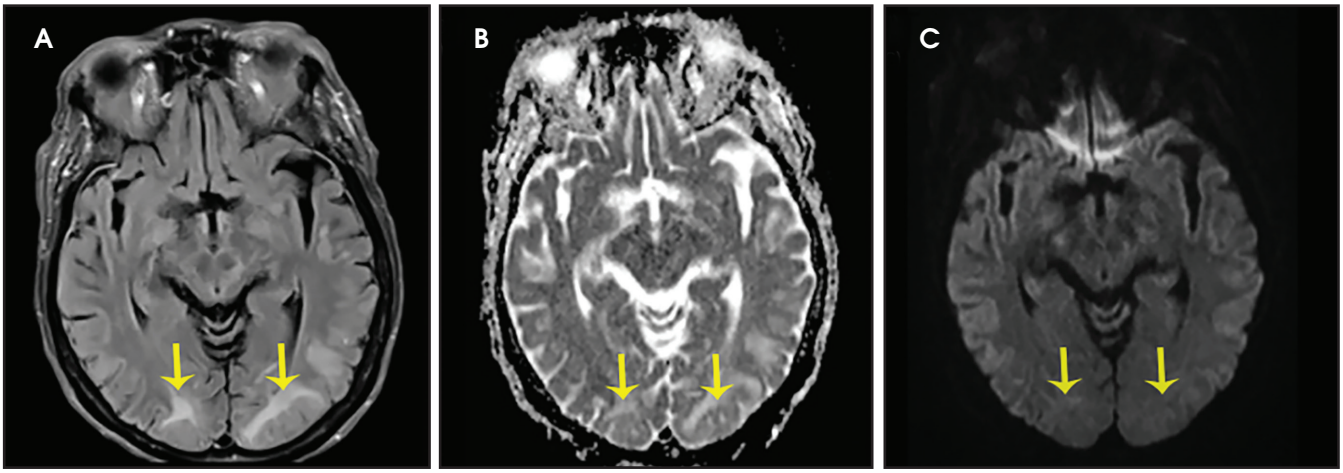

FIGURE 5. *49-year-old under tacrolimus treatment after bone marrow transplant presented with headaches and visual disturbances. (A) Axial FLAIR demonstrates bilateral hyperintense signal in the occipital subcortical white matter (yellow arrows). (B) ADC and (C) DWI show facilitated, not restricted, diffusion (yellow arrows).*

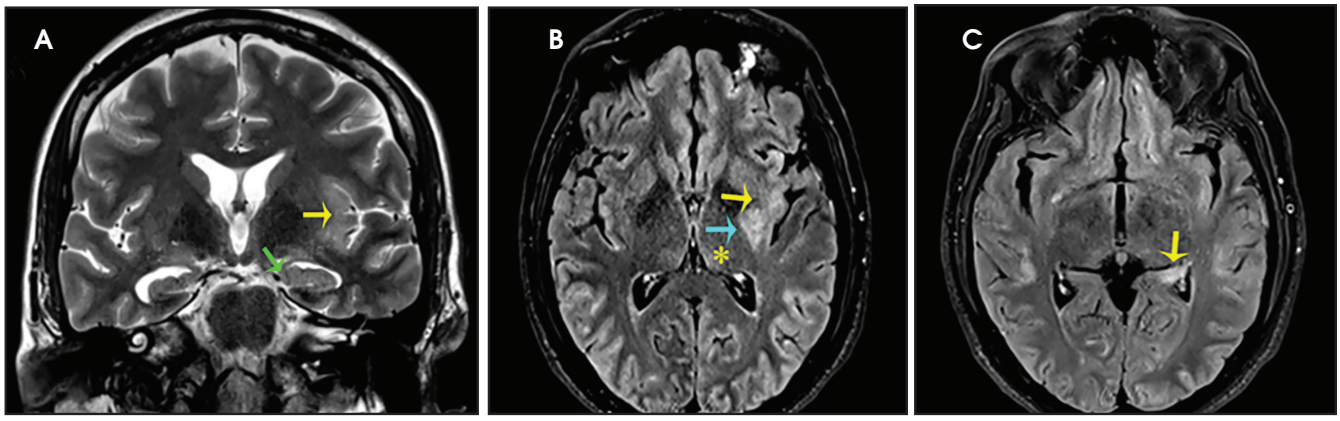

FIGURE 6. *45-year-old with a history of severe headaches, visual hallucinations, and cognitive dysfunction. Anti-TPO-AB and anti-TG-AB were elevated in CSF, indicating Hashimoto encephalopathy. (A) Coronal T2WI demonstrates abnormal hyperintense signal in the left insula (yellow arrow) and hippocampus (green arrow). (B) Axial FLAIR image demonstrates abnormal hyperintense signal in the left insula, subinsular white matter (yellow arrow), posterior putamen (blue arrow), and ipsilateral thalamus (yellow asterisk). C) Axial FLAIR image shows abnormal hyperintense signal of the isthmus of the cingulate gyrus (yellow arrow).*

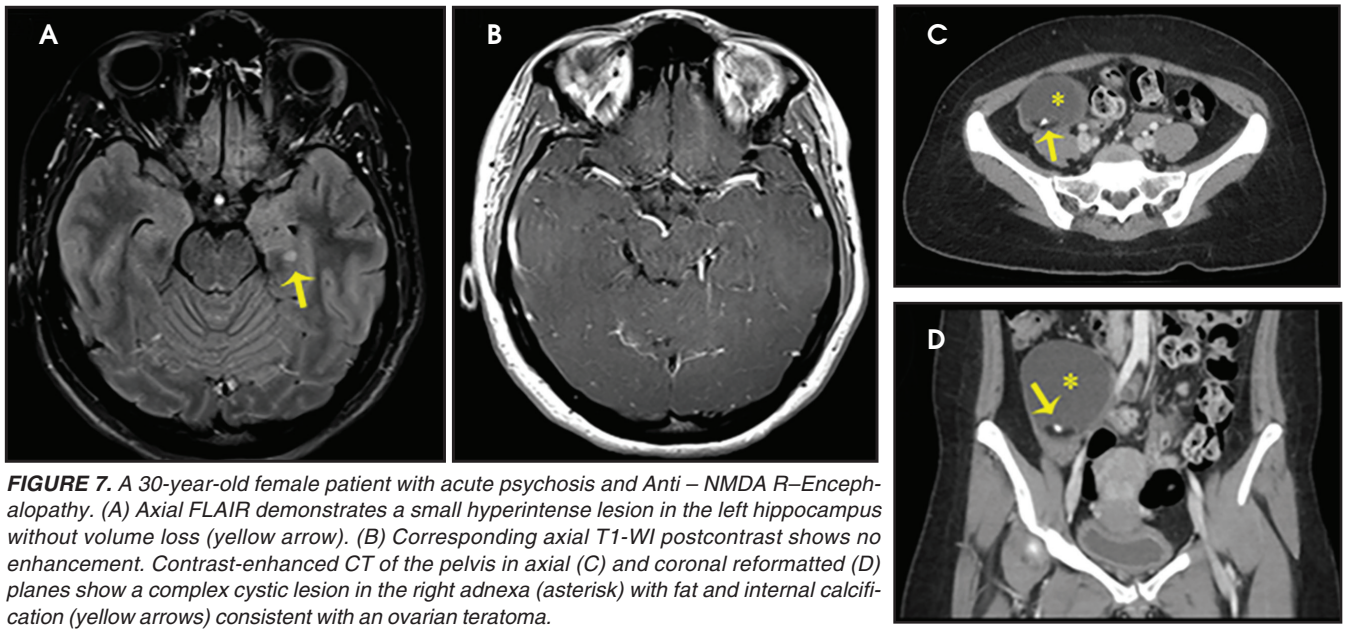

FIGURE 7. *A 30-year-old female patient with acute psychosis and Anti – NMDA R–Encephalopathy. (A) Axial FLAIR demonstrates a small hyperintense lesion in the left hippocampus without volume loss (yellow arrow). (B) Corresponding axial T1-WI postcontrast shows no enhancement. Contrast-enhanced CT of the pelvis in axial (C) and coronal reformatted (D) planes show a complex cystic lesion in the right adnexa (asterisk) with fat and internal calcification (yellow arrows) consistent with an ovarian teratoma.*

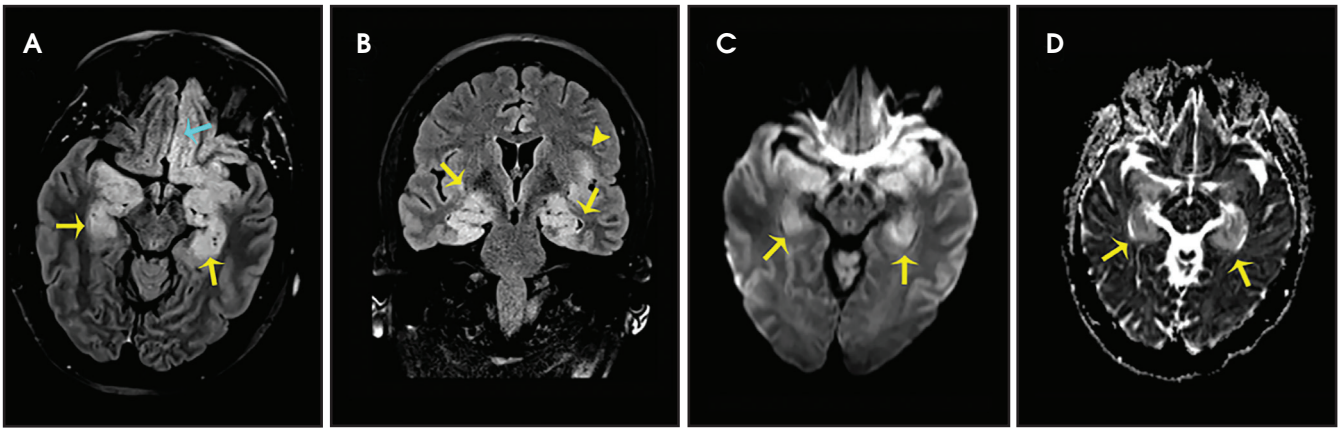

FIGURE 8. *60-year-old with history of small cell lung carcinoma presented with altered mental status and seizures, diagnosed with limbic encephalitis. (A) Axial and (B) coronal FLAIR images show abnormal signal hyperintensities in the left orbitofrontal (blue arrow), left insula (yellow arrowhead) and bilateral medial temporal lobes (yellow arrows). (C) DWI and corresponding ADC map (D) demonstrate bright signal due to T2 shine-through and increased diffusivity, respectively (yellow arrows).*

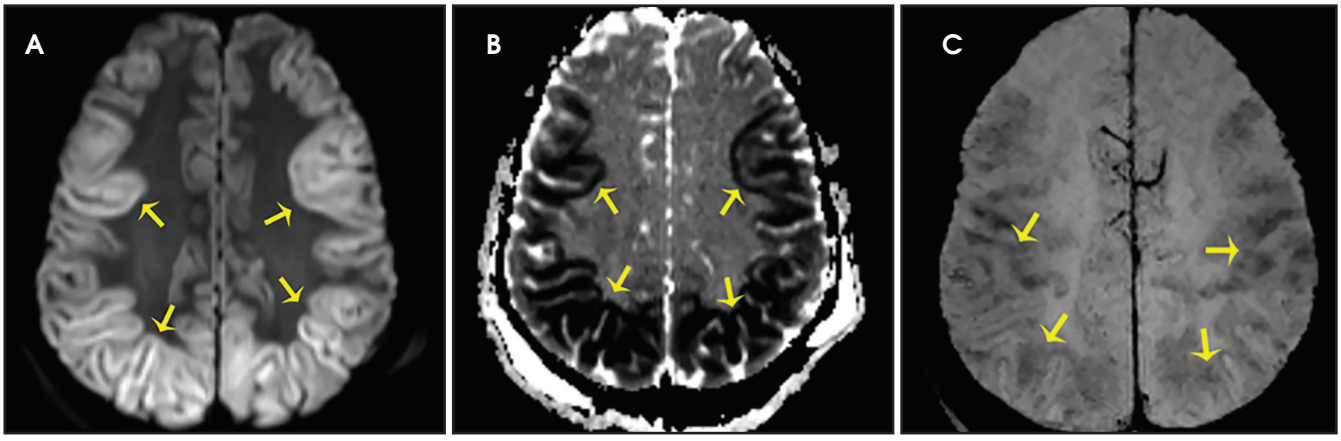

FIGURE 9. *33-year-old was brought to the hospital after a motorcycle collision, cardiac arrest and prolonged CPR, resulting in hypoxic encephalopathy. (A) Axial DWI and ADC map (B) demonstrate restricted diffusion of bilateral frontal and parietal cortices (yellow arrows). (C) Axial susceptibility weighted imaging demonstrates symmetrical bi-hemispheric pseudo-diminished cortical veins, and faint cortical low signal attenuation representing cortical laminar necrosis (yellow arrows).*

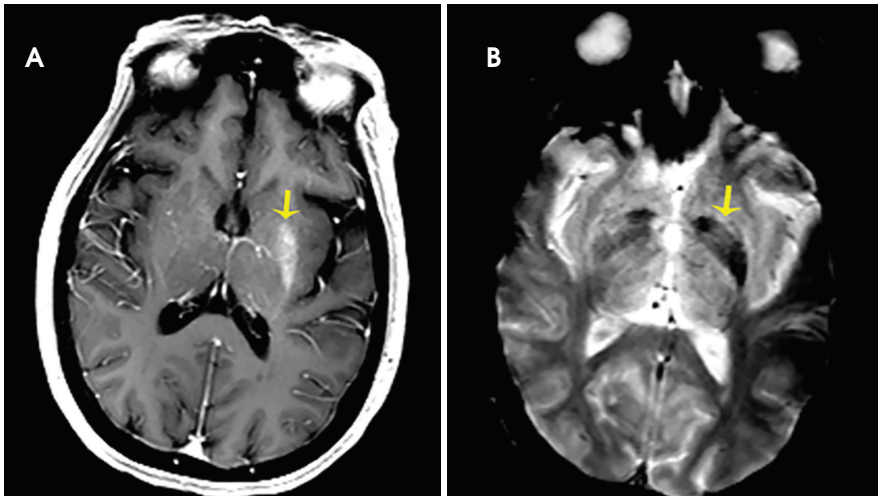

FIGURE 10. *57-year-old with uncontrolled diabetes mellitus presented to hospital after 1 week of involuntary movements of the right arm, diagnosed with nonketotic hyperglycemic hemichorea. (A) T1-WI postcontrast in axial view shows asymmetric abnormal hyperintensity mainly in the left putamen (yellow arrow). (B) Corresponding axial T2 gradient echo sequence demonstrates low signal intensity in the left putamen (yellow arrow).*

affected.[1] DWI usually identifies hyperintensities within one hour after insult, followed by increased signal intensities on T2-WI after 24 h. After 21 days, laminar necrosis of the cortex corresponds to T1 shortening (Figure 9).[1]

Nonketotic hyperglycemic hemichorea

Nonketotic hyperglycemic hemichorea is a rare treatable manifestation of diabetes mellitus usually involving the unilateral or, more commonly, bilateral caudate nuclei and the putamina.[1] It clinically presents with involuntary movements with elevated blood glucose levels and absence of ketones. T1-WI shows increased signal intensities of the involved structures with variable imaging findings on T2-WI (Figure 10).[1]

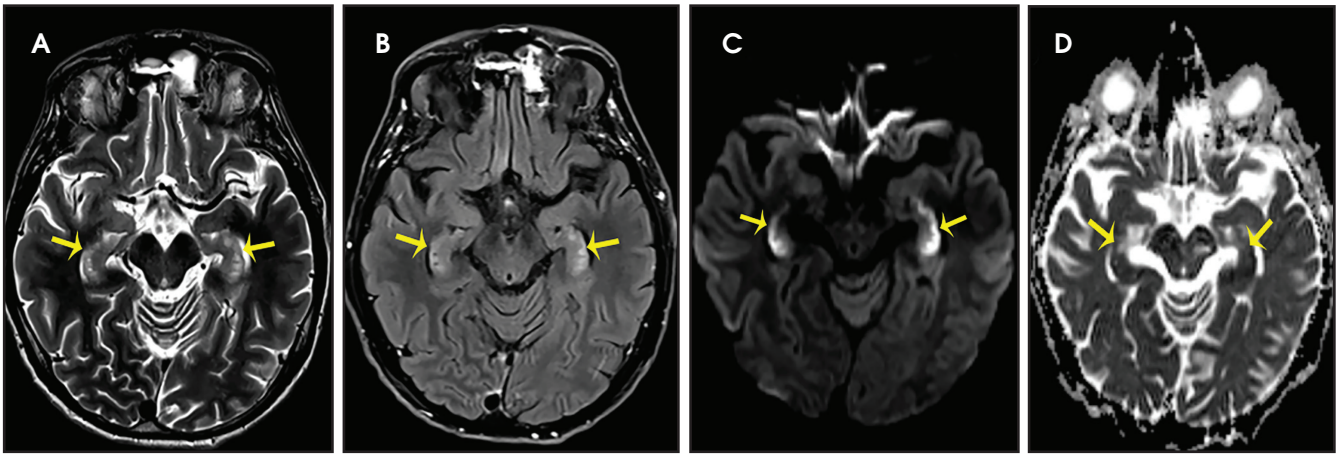

FIGURE 11. *35-year-old patient was brought to the hospital after trauma and hypoglycemia, diagnosed with hypoglycemic encephalopathy. (A) Axial T2-WI, and (B) FLAIR demonstrate abnormal hyperintense signal and corresponding restricted diffusion on (C) DWI and (D) ADC map in the cortical aspect of the bilateral hippocampi (yellow arrows).*

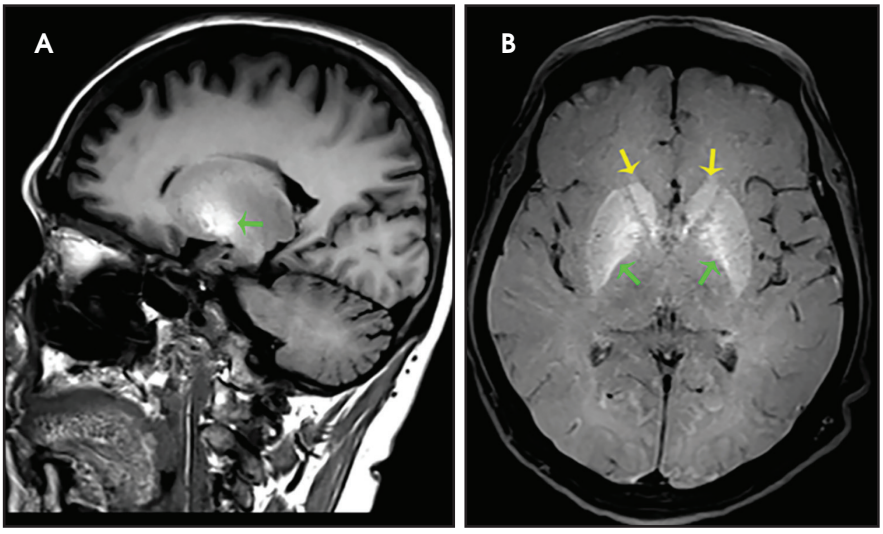

FIGURE 12. *A 57-year-old with history of hepatitis C complicated by cirrhosis with altered mental status, diagnosed with hepatic encephalopathy. (A) Sagittal T1-WI and (B) axial T1-WI non-contrast, with fat suppression demonstrate diffuse symmetric abnormal hyperintensities in the bilateral caudate (yellow arrows) and lentiform nuclei (globi pallidi and putamina) (green arrows).*

Hypoglycemic Encephalopathy

Decreased serum glucose levels lower than 50 mg/dl are most commonly associated with an unintentional overdose of sulfonylurea drugs or insulin in diabetics. Cerebral structures affected are the cortex, hippocampus, and basal ganglia, but involvement may be limited to white matter structures of the corpus callosum, internal capsule, and corona radiata in milder cases.[1] Bilateral T2 hyperintensity with restricted diffusion on DWI are characteristic imaging findings and involvement of the basal ganglia yields a less optimistic prognosis of this potentially reversible condition (Figure 11).[1]

Hepatic Encephalopathy (HE)

HE, which entails a wide range of symptoms owing to liver dysfunction such as cirrhosis and subsequent increase

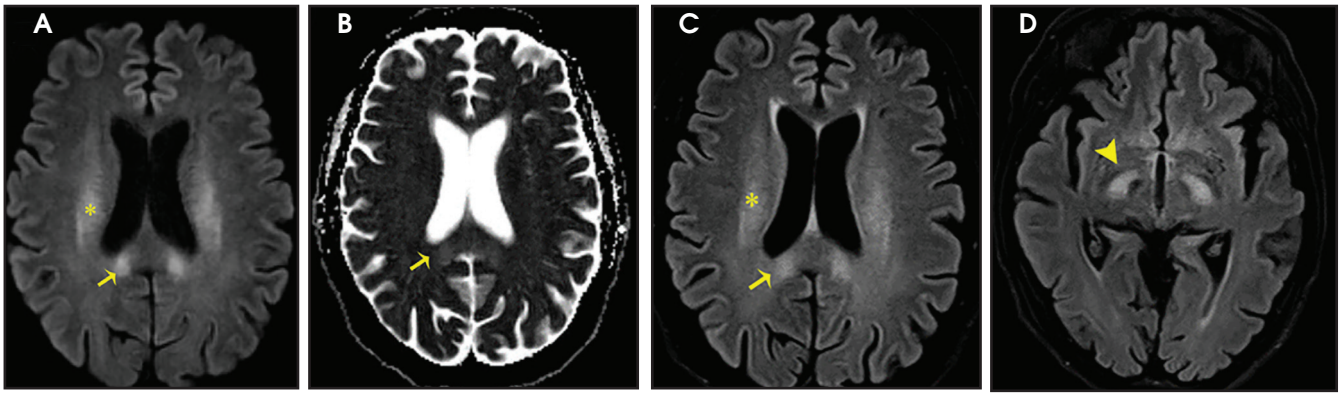

FIGURE 13. *44-year-old patient with a history of chronic alcohol use was admitted to the hospital with an acute alcohol intoxication, elevated serum ammonia levels (170 µg/dL), and diagnosed with hepatic encephalopathy. (A) Axial DWI, (B) ADC map, and (C and D) FLAIR images demonstrate abnormal symmetric hyperintense signal of the bilateral corticospinal tracts, coronae radiata (asterisk), cerebral peduncles (arrow head) and the splenium of the corpus callosum (arrows).*

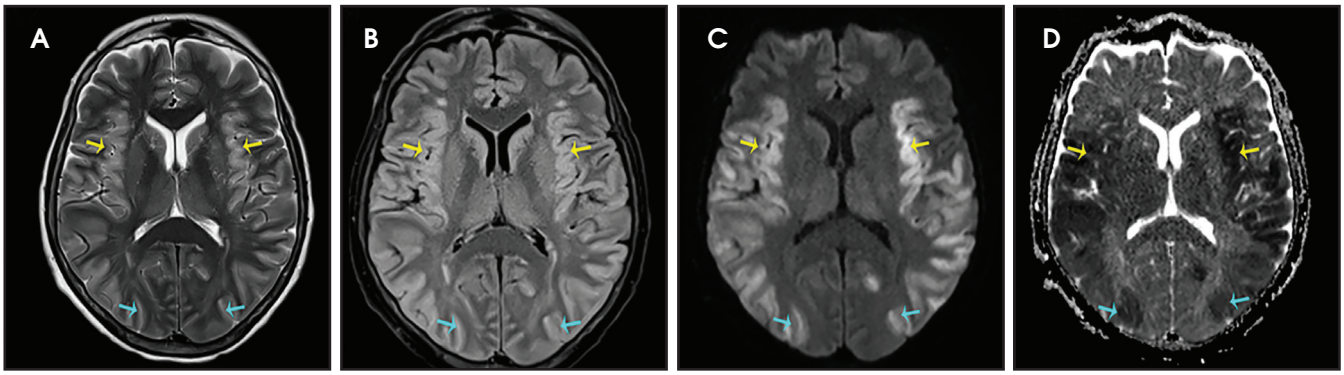

FIGURE 14. *65-year-old patient with decompensated hepatitis C cirrhosis was admitted to the hospital with seizures and decreased level of consciousness. Serum ammonia levels were elevated (330 µmol/L), and diagnosis of hyperammonemic encephalopathy was made. (A) Axial T2-WI, (B) FLAIR, (C) DWI, and (D) ADC map demonstrate abnormal T2 hyperintensity and restricted diffusion, respectively, of the insular cortex (yellow arrows), thalamus, and temporal-occipital cortical regions (blue arrows).*

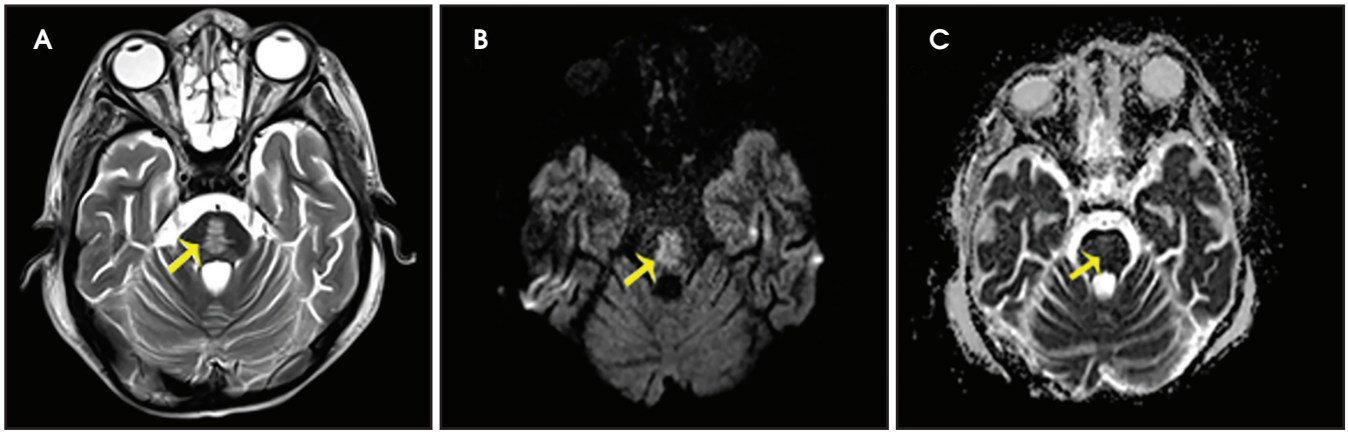

FIGURE 15. *4-year-old patient aggressively treated with fluids and bicarbonate due to metabolic acidosis after cardiac arrest, which resulted in hypernatremia and development of central pontine myelinolysis. MR images were obtained a few days after event. (A) Axial T2-WI shows a trident-shaped hyperintensity in the central pons (yellow arrow). (B) DWI demonstrates abnormal hyperintense signal in the central pons (yellow arrow). (C) ADC map with no signal dropout, findings are consistent with T2 shine-through (yellow arrow).*

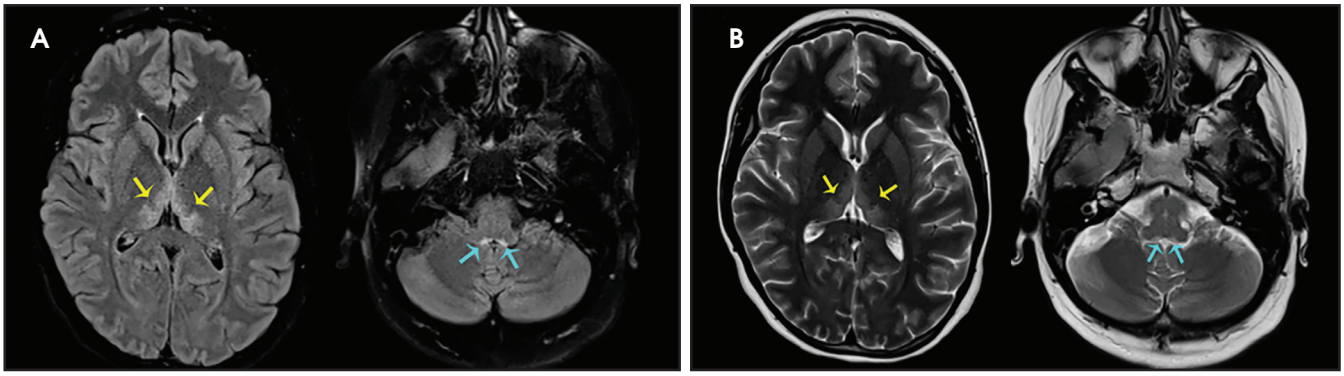

FIGURE 16. *A 23-year-old with decreased vision and history of alcohol use, diagnosed with Wernicke encephalopathy. (A) Axial FLAIR images and (B) axial T2-WI images demonstrate abnormal bilateral hyperintensities involving the ventromedial aspect of the thalami (yellow arrows) and the inferior cerebellar peduncles infratentorially (blue arrows).*

of usually metabolized substances, can present as an acute or chronic manifestation.[4] Acute HE is often fatal, while chronic HE can be relapsing or persistent with dementia, parkinsonism, and myelopathy dominating the clinical picture.[1] Involvement of the globi pallidi, subthalamic regions, and midbrain corresponding to hyperintensities on T1-WI, and T2 hyperintensity of the corticospinal tracts, the periventricular white matter, thalami, and internal capsules are characteristic imaging findings (Figures 12, 13).[1,4]

Hyperammonemic Encephalopathy

Ammonia may be elevated in advanced liver disease, manifesting as bilateral symmetric involvement of the insular cortex with restriction on DWI subsequent to astrocyte swelling, cell death, and edema (Figure 14).[1]

Central Pontine Myelinolysis / Osmotic Demyelination

The overly rapid correction of hyponatremia is the classic association, which initially presents as an altered sensorium and progresses to spasticity, and pseudo-bulbar palsy, as well as locked-in-syndrome, after 2-7 days.[1] Structures involved are the central pons, thalamus, putamen, and lateral geniculate bodies, with early restriction on DWI followed by hyperintensities on T2-WI and FLAIR sequences (Figure 15).[1,4]

Wernicke Encephalopathy (WE)

WE is related to thiamine (vitamin B1) deficiency, and the spectrum of affected patients includes alcoholics, as well as non-alcoholics with malabsorption syndromes or dietary deficits.[1] Onset is usually acute; however, only 16-38 % of all patients present with the typical triad of ophthalmoplegia, ataxia, and altered consciousness.[1] Structures involved are the medial thalami, mammillary bodies, the periaqueductal region, the floor of the fourth ventricle, and the tectal plate corresponding to hyperintensities on T2-WI (Figure 16).[1]

Summary

The brain is highly susceptible to toxins, autoimmune disorders, and metabolic changes, which can result in a broad range of encephalopathies. Signs are often nonspecific and can range from a hyper-alert agitated state, to coma, and death. Therefore, clinical assessment alone is often inconclusive. MR imaging is the modality of choice and frequently provides the first indication an encephalopathy as a possible cause of symptoms. By recognizing distinct imaging features, such as symmetry, characteristic topographic distribution, and enhancement patterns of the lesions, the radiologist plays a crucial role in narrowing the diagnosis to help improve patient outcome in an interdisciplinary approach.

References

1. Bathla G, Hegde AN. MRI and CT appearances in metabolic encephalopathies due to systemic diseases in adults. *Clin Radiol*. 2013;68(6): 545-554.
2. Olivas-Chacon CI, Treviño-Garcia M, Chua-Tuan JJ, et al. Leukoencephalopathic changes on magnetic resonance imaging associated with a thermogenic dietary supplement (Thermatrim). *Baylor University Medical Center Proceedings* 2015;28(3);389-391.
3. Rubinstein D, Edward E, James PK. Methanol intoxication with putaminal and white matter necrosis: MR and CT findings. *Am J Neuroradiol*. 1995;16(7):1492-1494.
4. Sharma P, Eesa M, Scott JN. Toxic and acquired metabolic encephalopathies: MRI appearance. *Am J Roentgenol*. 2009;193(3):879-886.
5. Keogh CF, Andrews GT, Spacey SD, et al. Neuroimaging features of heroin inhalation toxicity: "chasing the dragon". *Am J Roentgenol*. 2003;180(3):847-850.
6. Tamrazi B, Almast J. Your brain on drugs: imaging of drug-related changes in the central nervous system. *Radiographics*. 2012;5;32(3):701-719.
7. Shimono T, Miki Y, Toyoda H, et al. MR imaging with quantitative diffusion mapping of tacrolimus-induced neurotoxicity in organ transplant patients. *Eur Radiol*. 2003;13(5):986-993.
8. Ramalho, J, Mauricio C. Hashimoto's encephalopathy. *Radiol Case Rep*. 2016;6(1): 445.
9. Barry H, Byrne S, Barrett E. Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. *BJPsych Bull*. 2015; 39(1):19-23.
10. Urbach H, Soeder BM, Jeub M, et al. Serial MRI of limbic encephalitis. *Neuroradiology*. 2006;48(6):380-386.