Original Research Paper

Volume - 15 | Issue - 08 | August - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Radio-Diagnosis

MAGNETIC RESONANCE IMAGING OF EXCITOTOXIC BRAIN INJURY

Dr. Dhananjay D Ghodke — Professor, Department Of Radiodiagnosis, MGIMS, Sewagram, Wardha, Maharashtra, India.

Dr. Sumedh S Meshram* — Junior Resident, Department Of Radiodiagnosis, MGIMS, Sewagram, Wardha, Maharashtra, India *Corresponding Author

ABSTRACT **Background And Purpose Of The Study:** Neuronal damage brought on by excitotoxic amines mediated by intrinsic neuronal seizure activity is a hallmark of excitotoxic brain injury. Cytotoxic edema is the ultimate result of these excitotoxic processes. The cornerstone of neuroimaging is magnetic resonance imaging (MRI), which can identify cytotoxic edema early on. These conditions encompass infarction, hypoxic ischemic encephalopathy (HIE), the initial phase of Wallerian and trans-neuronal degeneration, shaken baby syndrome, status epilepticus, lesions of the corpus callosum related to seizures or antiepileptic medications, diffuse axonal injury, toxic or metabolic encephalopathies, the acute phase of multiple sclerosis, and Creutzfeldt-Jakob disease (CJD). This study aims to assess and understand excitotoxic brain damage patterns across a range of neurological diseases. Status epilepticus, hypoxia ischemic encephalopathy, and corpus callosum lesions associated with seizures or antiepileptic medications are among these conditions. **Materials And Methods:** MRI Brain of patients with various patterns of excitotoxic brain injury was performed & analysed on 1.5 Tesla Siemens Magnetom Avanto MRI machine. There patterns were further studied & clinically correlated. **Conclusion:** Neuroimaging is a critical component of the evaluation of excitotoxic brain injury. It provides diagnostic value in many cases and in helps in emergent interventions that would not have been possible otherwise.

KEYWORDS : excitotoxic brain injury, cytotoxic edema, status epilepticus, multiple sclerosis, metabolic encephalopathies, diffuse axonal injury.

INTRODUCTION:

Excitotoxic brain injury represents a distinct form of transsynaptic brain injury induced by excitotoxic amines. The receptors associated with these injuries are extensively distributed throughout the brain parenchyma, encompassing both gray matter (neurons and astrocytes) and white matter (astrocytes, oligodendrocytes, myelin sheaths, and axons). (1)

This review aims to illustrate and elucidate the excitotoxic mechanisms involved in various acute neurological conditions. These conditions encompass infarction, hypoxic ischemic encephalopathy (HIE), the initial phase of Wallerian and trans-neuronal degeneration, shaken baby syndrome, status epilepticus, lesions of the corpus callosum related to seizures or antiepileptic medications, diffuse axonal injury, toxic or metabolic encephalopathies, the acute phase of multiple sclerosis, and Creutzfeldt-Jakob disease (CJD). Excitotoxic brain injury is regarded as a final common pathway for numerous neuropathological conditions, leading to cytotoxic edema. Diffusion-weighted (DW) imaging is particularly valuable for the early identification of cytotoxic edema, appearing as an area of abnormal hyperintensity linked to a reduced apparent diffusion coefficient (ADC).

Neuroimaging is advised for patients with excitotoxic brain injury, with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) serving as the primary modalities, where MRI demonstrates a higher diagnostic yield. Magnetic Resonance Imaging (MRI) is more effective than Computed Tomography (CT) in detecting inflammatory changes or subtle, remote structural abnormalities.

EXCITOTOXIC INJURY MECHANISMS:

Predominantly, excitatory amino acids include glutamate, aspartate and glycine. These contribute to about 50 % of all synaptic processes. The most important of these is Glutamate, which supervises various parts of the human brain, such as memory, movement, feeling, and thinking. (2)

Recent research indicates receptors associated with excitotoxic processes are extensively found throughout the brain, present in both gray matter (neurons and astrocytes) and white matter (astrocytes, oligodendrocytes, myelin sheaths, and axons) Glutamate causes damage or death of neurons in pathological conditions, particularly by stimulating the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Glutamate is released from the presynaptic terminal of neuronal axons into the synaptic gap and subsequently functions as a neurotransmitter (Fig 1).

The surplus glutamate attaching to NMDA receptors permits the influx of Calcium ions into the postsynaptic neuron, leading to necrotic cell death or apoptosis, while the overabundance of glutamate attaching to non-NMDA receptors permits Na+ to enter the postsynaptic neuron, causing cytotoxic edema. Due to the presence of these receptors in glial cells, the overstimulation by glutamate causes swelling of glial cells, which appears to safeguard cells neurons from excitotoxic brain injury.

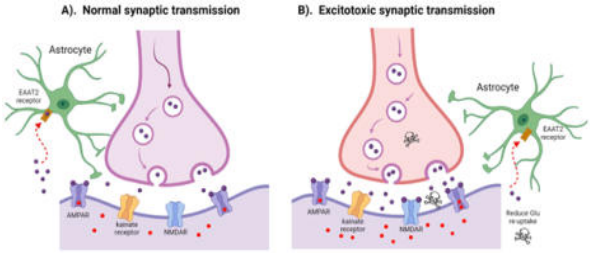


Figure 1. Physiologic Versus Excitotoxic Synaptic Glutamate Transmission And Re-uptake.

Increased extracellular glutamate is a direct cause of excitotoxic brain injury. In acute excitotoxic injury, excessive extracellular glutamate results from decreased reuptake energy failure, increased release by excessive depolarization of neuronal membranes.

Acute excitotoxic injury can also be related to functional failure of the glutamate receptor and the presence of substances structurally similar to glutamate, such as hydroxyglutarate at the receptor sites.

Excessive extracellular glutamate depolarizes injured adjacent glial cells or neurons and in turn causes release or leakage of glutamate. This mechanism is self-propagating through neuron-glial cell units and through trans-axonal or trans-synaptic routes along the white matter fibre tracts.

Increased extracellular glutamate is a direct cause of excitotoxic brain injury in various conditions which include status epilepticus, brain infarction, hypoxic ischemic encephalopathy, wallerian degeneration, shaken baby syndrome, diffuse axonal injury and toxic demyelinating degenerative disease.

Excitotoxic mechanism mediated by intrinsic neuronal seizure activity. The intrinsic neuronal activity increases the release of glutamate from presynaptic terminals. Excessive glutamate binds to NMDA and non-NMDA receptors, causing cell swelling and damage in neurons and glial cells, which leads to cell death or selective neuronal damage. Astrocytes detoxify excessive glutamate which helps in repair at cellular & tissue level.

In acute phases, the reactive astrocytes cause cytotoxic edema which is responsible for reversible hyperintensities on DWI & ADC sequences.

AIMS & OBJECTIVES OF THE STUDY:

Main objective of the study was to illustrate and describe various patterns of excitotoxic brain injury and the role of diffusion weighted imaging (DWI) in it's early detection.

MATERIALS & METHODS:

Type of study: Retrospective study.
Place of study: Department of Radiodiagnosis in a tertiary care hospital.
Machine used: 1.5 Tesla Siemens Magnetom Avanto MRI machine.

Various Patterns Of Excitotoxic Brain Injury

Hypoxic Ischemic Encephalopathy

In HIE, the depletion of energy in neurons and glial cells results in a reduced reuptake of glutamate, consequently leading to an increase in extracellular glutamate. The prevalence of HIE varies between adults and children. During the perinatal phase, the developing brain is especially susceptible to excitotoxic damage. NMDA receptors are predominant in the immature brain, where synaptic transmission is both inefficient and highly plastic. The rapid rate of myelination and synapse formation (synaptogenesis) may contribute to the susceptibility to ischemic injury. The tendency for lesions to occur in the putamen, thalamus, and peri-Rolandic cerebral cortex in severe HIE aligns with regions vulnerable to energy failure. A potentially significant connection among these areas is their linkage through excitatory circuits (3). Thus, excessive activity in one area of these excitatory pathways could spread to other regions via their synaptic connections.

DW imaging effectively illustrates lesions in the basal ganglia and white matter, as well as along the corticospinal tract and corpus callosum (Figs 2-3) (4).

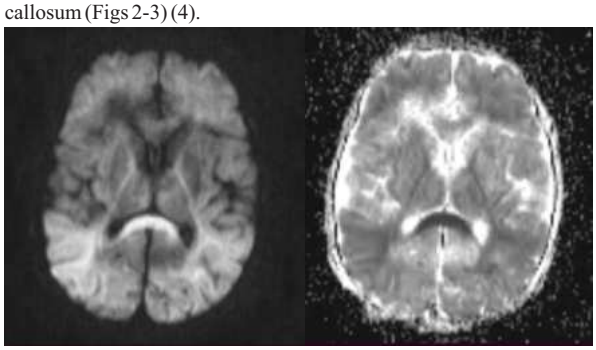


Fig 2 & 3- DW images show diffuse hyperintensity with decreased ADC in splenium of corpus callosum, internal capsules, thalami, and white matter. This distribution may be related to excitatory circuits. The neonatal brain seems to be highly vulnerable to acute excitotoxic injury.

DIFFUSE AXONAL INJURY

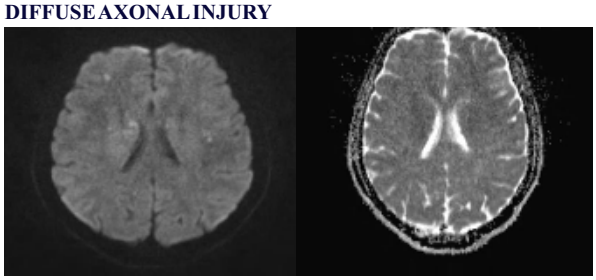


Fig 3 & 4: DW images show lesions in right frontal gray-white matter junction & caudate nucleus which appear hyperintense on DWI with decreased ADC; they represent cytotoxic edema presumably due to the leakage of glutamate from the axon.

Diffuse axonal injury is believed to result from excitotoxic processes, especially those related to glutamate and NMDA receptors (5). Damage to axons frequently occurs at the node of Ranvier, which is a brief segment between the myelin sheaths (extensions of oligodendrocytes), leading to a traumatic disruption in the axonal membrane; this disruption permits the escape of glutamate into the extracellular environment (6). The astrocytic end-foot, situated on the axon at the node of Ranvier, may offer protection to the axons. An excess of extracellular glutamate results in axonal swelling and cytotoxic edema of glial cells, potentially contributing to diffusion irregularities that lead to necrosis, axonal degeneration, and gliosis. DW imaging reveals hyperintense lesions correlated with reduced ADC. This is commonly observed in the corpus callosum, fornix, gray matter–white matter junction, and brainstem (including cerebellar peduncles) (7) (Fig 3-4).

HERPES ENCEPHALITIS

In cases of acute encephalitis, there is a notable increase in the levels of glutamate and glycine within the cerebrospinal fluid (CSF) (8). This finding indicates that an excitotoxic mechanism may contribute to neuronal damage observed in herpes encephalitis. The excessive release of glutamate, which is triggered by free radicals produced during the immune response to infections, could be the initiating factor for excitotoxicity. The occurrences of herpes encephalopathy are likely associated with the susceptibility of the neonatal brain to excitatory amines. Furthermore, the manifestation of herpes encephalitis varies depending on the patient's age. In older children and adults, herpes simplex type encephalitis typically affects the medial temporal lobes, inferior frontal lobes, and insula. Diffusion-weighted imaging reveals signal intensity abnormalities in these regions (Fig 5-6).

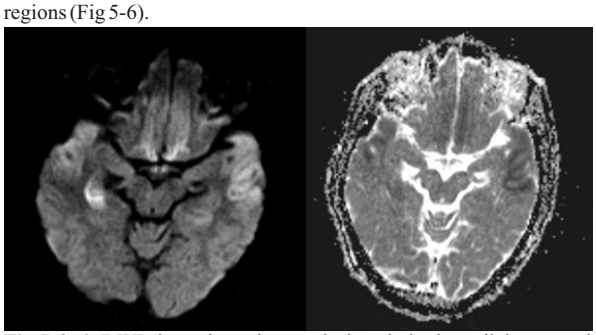
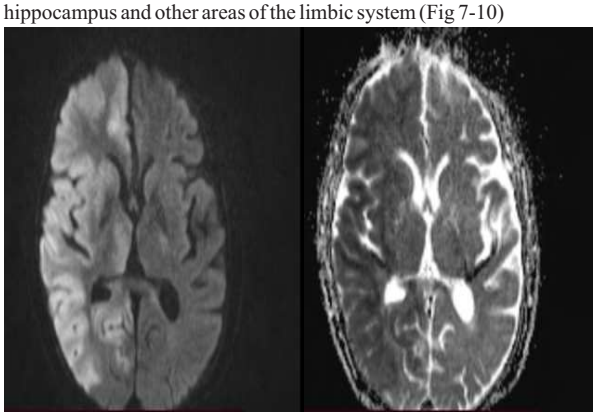


Fig 5 & 6- DWI shows hyperintense lesions in both medial temporal lobes with low ADC values representing excitotoxic brain injury.

Status Epilepticus

In status epilepticus, neuronal damage primarily arises from an excitotoxic mechanism driven by intrinsic neuronal seizure activity (9). During this condition, neuronal seizure activity enhances the release of glutamate from the presynaptic terminals of neuronal axons. An excess of glutamate traverses the synaptic cleft to attach to NMDA and non-NMDA receptors, resulting in cytotoxic edema in both neurons and glial cells, which can lead to apoptosis or selective neuronal necrosis. Astrocytes are crucial for cellular and tissue repair as they detoxify the surplus glutamate (10, 11). The cytotoxic edema observed in reactive astrocytes during the acute phase is thought to be responsible for the reversible signal intensity abnormalities (12).

Encephalopathy associated with status epilepticus frequently affects the hippocampus, various regions of the limbic system, the thalamus, and the cerebellum. This pattern of lesions observed in diffusion-weighted imaging appears to correlate with the distribution of NMDA-type glutamate receptors, which are predominantly found in the hippocampus and other areas of the limbic system (Fig 7-10)



DWI shows hyperintense lesions in right cerebral hemisphere, right caudate nucleus & right thalamus with low ADC values representing excitotoxic brain injury in a patient of status epilepticus

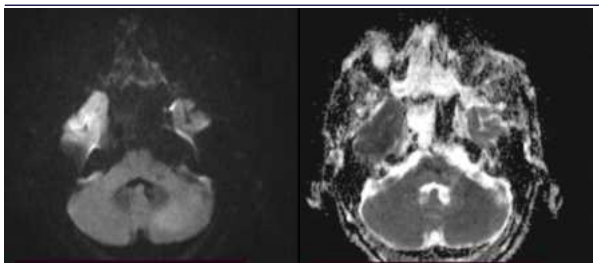


Fig 7-10: DWI shows hyperintense lesions in left cerebellar hemisphere with low ADC values representing

"**Crossed cerebellar diaschisis**" in excitotoxic brain injury in a patient of status epilepticus.

Focal Lesion In The Splenium Of The Corpus Callosum

A distinct area of diffusion abnormality has been identified in the splenium of the corpus callosum during the immediate postictal phase. The potential causes of a focal lesion in the corpus callosum are thought to include seizures, medications, or a combination of both (13 –15). The transhemispheric spread of seizure activity may contribute to transient focal edema. Seizure activity travels through the splenial callosal fibers to the opposite hemisphere. The splenium houses decussating fibers that originate from the temporal lobes; these fibers are likely responsible for the intrahemispheric spread of seizure activity that begins in the temporal-lobe focus. Additionally, transient focal edema in the splenium of the corpus callosum can occur following the sudden withdrawal or reduction of antiepileptic medications such as phenytoin, carbamazepine, and vigabatrin (14). This phenomenon is influenced by the effects of antiepileptic drugs on fluid-balance systems, particularly the arginine-vasopressin system (15). Seizure activity or the impact of medications may result in excitotoxic injury, leading to reversible cytotoxic edema in astrocytes or myelin sheaths. Research has shown a significant presence of glutamate receptors and elevated enzymatic activity in the corpus callosum (16). Diffusion-weighted imaging reveals an acute lesion in the splenium as hyperintense with reduced ADC (Fig 11-12) (17).

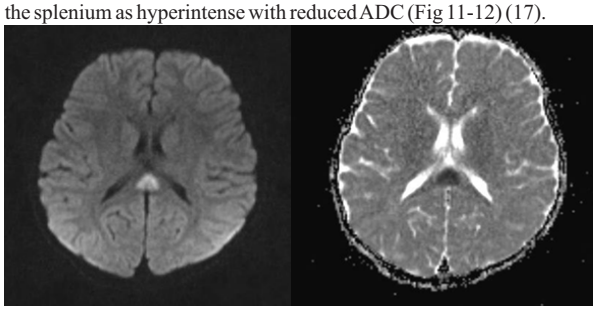


Fig 11 & 12- DWI shows hyperintense area in splenium of corpus callosum showing low ADC value, representing transient lesion of splenium of corpus callosum.

OSMOTIC MYELINOLYSIS

Central pontine myelinolysis and extrapontine myelinolysis signify the degeneration of myelin sheaths in specific regions of the brainstem and cerebrum.Organic osmolytes such as glutamate, glutamine, betaine, or taurine have been associated with the development of myelinolysis resulting from the rapid correction of severe hyponatremia (18). Pathological observations reveal the destruction of myelin sheaths, while the nerve cells and axons remain relatively intact. Diffusion-weighted imaging can illustrate the lesions in the initial phase as hyperintense with reduced ADC, indicating cytotoxic edema (Fig 13-14).

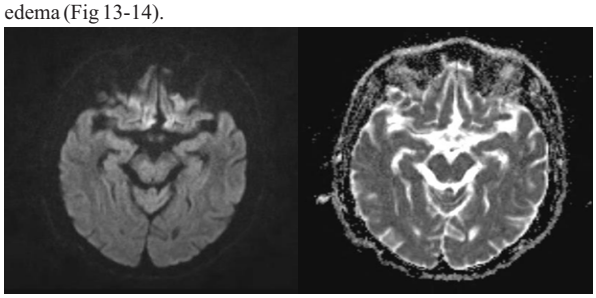


Fig 13-14: DW images show this lesion a hyperintense with mildly decreased ADC. This finding represents cytotoxic edema seen in the early phase of central pontine myelinolysis

TOXIC/METABOLIC Encephalopathy

Microvascular occlusion is regarded as one of the factors contributing to white matter ischemic alterations in metabolic encephalopathy. Glutamate excitotoxicity has the potential to harm myelin sheaths and axons. NMDA receptor antagonists may offer protection against glutamate neurotoxicity (19). MR imaging reveals diffuse or multifocal white matter lesions that appear hyperintense on T2-weighted images. Diffusion-weighted imaging during the acute phase of the disease demonstrates diffuse hyperintensity accompanied by reduced ADC in the white matter.

Thiamine (vitamin B1) deficiency can lead to Wernicke encephalopathy, which is characterized by confusion, ataxia, abnormal eye movements, and visual impairment. In the absence of thiamine, the Krebs and pentose phosphate cycles are unable to effectively metabolize glucose (20). This enzymatic inactivity results in the accumulation of intracellular glutamate. Consequently, cellular homeostasis is disrupted, leading to the release of glutamate into the extracellular environment (21).

Pathological findings include demyelination, edema, astrocytic swelling, and necrosis in the mammillary bodies, thalamic and hypothalamic nuclei, periaqueductal gray matter, the walls of the third ventricle, the floor of the fourth ventricle, and, less frequently, the caudate nuclei, frontal, and parietal cortex. With the administration of intravenous thiamine, these lesions may resolve. Diffusion-weighted imaging depicts these lesions as hyperintense with either decreased or increased ADC. Lesions exhibiting decreased ADC are believed to indicate cytotoxic edema of neurons or astrocytes, while those with increased ADC may signify vasogenic edema (Fig- 15-16) (22-24).

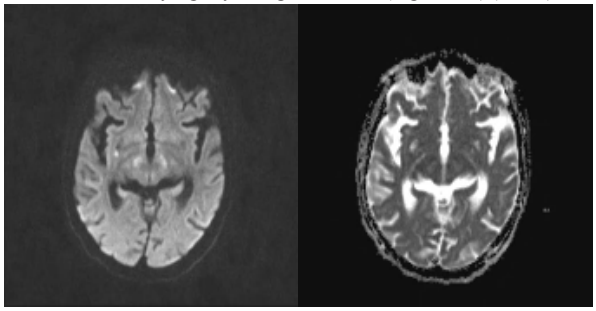


Fig 15 & 16- DW image shows hyperintense lesions with decreased ADC in the hypothalami that may represent excitotoxic brain injury. Release of glutamate into the extracellular space may cause lesions in Wernicke encephalopathy.

MULTIPLE SCLEROSIS

Glutamate excitotoxicity affects not only neurons and astrocytes but also oligodendrocytes, myelin sheaths, and axons (25). The levels of glutamate and aspartate are elevated in the cerebrospinal fluid (CSF) of individuals diagnosed with acute multiple sclerosis (26). An immunohistochemical investigation revealed that active lesions in multiple sclerosis exhibited significant glutamate production in macrophages and microglia located near regions of axonal injury (27). The excitotoxic effects on oligodendrocytes, myelin sheaths, and axons may lead to the formation of cytotoxic plaques. These cytotoxic plaques are infrequent and are likely observed during the hyperacute or acute stages of multiple sclerosis. They appear hyperintense on diffusion-weighted (DW) images, accompanied by a reduction in apparent diffusion coefficient (ADC) (Fig 17-18). The pathological characteristics of cytotoxic plaques primarily indicate the presence of intramyelinic edema.

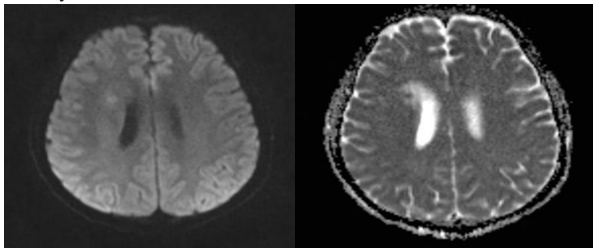


Fig 17 & 18- DW image shows hyperintense lesions in the

periventricular subcortical white matter with decreased ADC. They represent cytotoxic plaques presumably related to excitotoxic injury of oligodendrocytes, myelin sheaths, and axons

CREUTZFELDT-JAKOB DISEASE

CJD is classified as one of the prion diseases, which is marked by a rapid onset of dementia, myoclonus, and ataxia.Prion diseases are defined by the accumulation of misfolded prion proteins that are harmful to the endoplasmic reticulum. Recent reports have highlighted significant and selective abnormalities in glutamate receptors; these findings may account for the distinctive pattern of brain lesions observed in CJD (28).Diffusion-weighted (DW) imaging demonstrates greater sensitivity compared to traditional MR imaging in identifying abnormalities associated with CJD. In DW imaging, these lesions appear hyperintense and are frequently linked to a reduction in apparent diffusion coefficient (ADC) (29 –33).

BRAIN INFARCTION

During ischemia, cytotoxic edema primarily arises due to energy failure in neurons and astrocytes. It may spread into the penumbra region through neuron-glial cell units and synapses via excitotoxic mechanisms (34). Either energy failure or excitotoxic processes impair the sodium-potassium pump, permitting extracellular sodium and water to infiltrate the cell. An increase in intracellular calcium ion concentrations may initiate the production of proteases and lipases, leading to infarction, gliosis, or delayed neuronal loss. In experimental studies, NMDA-type glutamate receptor antagonists (MK-801) have been shown to diminish the volume of ischemic injury following occlusion of the middle cerebral artery (MCA) (35). This observation suggests that the pathophysiological characteristics of the ischemic penumbra are linked to excitotoxic damage associated with glutamate. Diffusion-weighted imaging reveals cytotoxic edema in ischemic lesions as hyperintense with reduced ADC, which may propagate into the ischemic penumbra due to excitotoxic mechanisms.

Other noteable conditions which result in excitotoxic brain injury include shaken baby syndrome, wallerian degeneration, phenylketonuria & methotrexate induced leucoencephaloapthy.

CONCLUSION:

MRI serves as the cornerstone of neuroimaging owing to its exceptional capability to identify excitotoxic edema. The primary mechanism of neuronal damage is excitotoxic brain injury. An excess of glutamate, resulting from heightened intrinsic neuronal activity, binds to NMDA receptors, leading to damage in neurons and glial cells. Reactive astrocytes induce reversible cytotoxic edema, which manifests as hyperintense signals on DWI with corresponding restrictions on ADC sequences in the thalamus, hippocampus, various regions of the limbic system, and the cerebellum, as NMDA receptors are predominantly located in these areas. Magnetic resonance imaging is fundamental in diagnosing excitotoxic brain injury.

DW imaging proves beneficial for assessing cytotoxic edema resulting from excitotoxic brain injury, a frequent endpoint for numerous neurological disorders. The severity (and potential reversibility) and distribution of this edema vary across different neurological diseases (considering cell types, initial insults, and their underlying mechanisms) and among patients of varying ages (influenced by factors such as the age-dependent distribution of receptors and the maturity of the blood-brain barrier). Excitotoxic amine receptors are found in neurons, axons, glial cells, and myelin sheaths. Astrocytes and myelin sheaths, which safeguard synapses and axons, swell upon absorbing excessive glutamate. This cytotoxic edema appears to be temporary and typically resolves upon subsequent MR imaging.

Energy failure, characterized by impaired glutamate reuptake, represents the initial insult during infarction and hypoxic-ischemic encephalopathy (HIE). This condition often leads to irreversible excitotoxic brain injury, culminating in necrosis and atrophy. Secondary degeneration, such as Wallerian degeneration, appears to be associated with excitotoxic circuits through synapses or axons.

An excessive release of glutamate can induce cytotoxic edema in scenarios such as seizures, infections, demyelination, and toxic metabolic disorders. This type of cytotoxic edema arises from excitotoxic injury with minimal energy failure; it occasionally resolves upon follow-up MR imaging. Diffuse axonal injury may result in the leakage of glutamate from the axons.

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