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Role of MRI in Evaluation of Various Encephalopathies and Leukoncephalopathies In Paediatric And Adult Population

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I. Introduction:-

Leukodystrophies, are a wide spectrum of inherited neurodegenerative disorders that affect the integrity of myelin in the brain and peripheral nerves. Most of these disorders are classified into lysosomal storage diseases, peroxisomal disorders, and diseases caused by mitochondrial dysfunction. Each leukodystrophy has distinct clinical, biochemical, pathological, and radiologic features [(1)].

The etiology of white matter lesions is very heterogeneous and includes congenital[(5)], vascular[(3,4)], inflammatory[(6,7)], neoplastic[(2,3)], neurodegenerative[(2,8,9)], metabolic[(10,11,12)], toxic [(13,14)]and traumatic origins.

The term "toxicleukoencephalopathy" encompasses a wide spectrum of diseases that may injure and cause structural alteration ofthe white matter with functional dysfunction[(15)]. Toxic encephalopathy includes a spectrum of symptomatology ranging from subclinical deficits to overt clinical disorders. The CNS is protected from toxic exposure to some extent, but it remains vulnerable to the effects of certain chemicals(lipophilic) found in the environment[(16)]. Toxic encephalopathy usually results in symmetrical involvement of the cortices and deep gray structures of the brain[(17)].

Vascular encephalopathies include Posterior reversible encephalopathy syndrome (PRES) and Hypoxic Ischemic encephalopathy. Hypertension (>150/100, commonly in patients with eclampsia) with resultant failed autoregulation and cerebral hyperperfusion due to cytokines from ischemic/necrotic tissue developing brain edema. Other casues of PRES include vasculopathy with endothelial dysfunction, drug induced[(18)].

II. Aims &Objectives: -

- To distinguish the MRI appearance of acute toxic leukoencephalopathy/ metabolic encephalopathy from another reversible entity
- To investigate if any predominant region of brain is affected specific to various causes of encephalopathy and leukoencephalopathy.
- Identify the imaging features of some of the most prevalent CNS toxic and metabolic disorders.
- Describe imaging findings that are highly specific for the diagnosis of particular toxic and metabolic brain disorders.

III. Material and Methods: -

Inclusion criteria:

- Patients referred to radiology department with a clinical suspicion of encephalopathy or leukoencephalopathy.

- Patients referred with sudden onset deterioration of neurological function and altered sensorium.
- Paediatric patients with suspected inborn error of metabolism, birth asphyxia sequelae or for evaluation of failure to thrive
- Only those patients willing to participate and giving informed consent for the study were included.

Exclusion criteria:
- Patient not willing to participate in the study.
- Parents not willing to provide consent for proper child sedation during MRI.

Study Guidelines:
The present study was carried out in the Department of Radiodiagnosis, in a tertiary care teaching hospital. patients who underwent MR imaging of Brain during the period between October 2021to January 2023 were randomly considered for this study.Relevanthistory of illness and clinicalfindings of allpatientswererecorded. WhileperformingMRIscan,sedation was given whenever necessary and sedativeswereusedunderthesupervisionofan anaesthetist according to the requirement.MRI was performed on 1.5 Tesla MRI scanning machine (Philips ACHIEVA 1.5T MRI Unit)using head coil.
Conventional MRI imaging was performed by taking axial T1, T2, fluid attenuated inversion recovery (FLAIR) and Diffusion-weighted, FLAIR images in coronal plane, T2 axial plane and also T1-weighted axial, sagittal and coronal post contrast images {gadolinium (dose 0.1mmol/kg) enhanced MRI}, MR spectroscopy was performed by using 2D/3DPRESSdepending on clinical suspicion.
The following features were assessed by MRI:
- Region of brain involved:

a) Gray matter/ White matter/Gray-White junction
b) Lobar involvement/ Deep nuclei/ Diffuse involvement/ Posterior fossa involvement.
- Behaviour of lesions on diffusion – Restricted/ Facilitated/ No restriction.
- Overall varieties of encephalopathies

a. Toxic (alcohol/ methanol/ drug induced)
b. Metabolic (hepatic/ hypoglycemic/ Wernicke's/ Marchifava-Bignami)
c. Vascular (HIE/ PRES)
d. Infectious (HIV/ TORCH/ Viral)

- Varieties of Leukoencephalopathies

a. Metachromatic Leukodystrophy
b. Canavan's Disease
c. Van Der Knapp's disease (Megalencephalic Leukoencephalopathy with subcortical cysts)
d. Progressive Multifocal Leukoencephaloapthy
e. Mitochondrial Leukoencephalopathy

IV. Observations and Results:-

1. Age wise Distribution

Age Group	No. of Cases	Percentage
0-18yrs	14	38.8%
19-30yrs	10	27.7%
31-45yrs	7	19.4%
>45yrs	5	13.8%

2. Gender wise distribution

Gender	No. of Cases	Percentage
Males	16	44.4%
Females	20	55.6%

3. Symptom wise Distribution

Symptoms	No. of Cases
Altered Sensorium	14
Seizures	8
Unconsciousness	4
Ataxia/ Cerebellar Signs	4
Fever	10
Failure to thrive/ Delayed Milestones	8

4. Cerebral Involvement

Involved on MRI	No. of Cases	Percentage
Solitary Hemisphere	4	11.2%
Deep Gray Matter	14	38.7%
Diffuse Involvement	6	16.5%
Posterior Fossa	4	11.2%
White Matter	8	22.4%

5. Appearance on Diffusion Sequences

Diffusion Pattern	No. of Cases	Percentage
Restriction	24	66.6%
Facilitated Diffusion	4	11.1%
No Restriction	8	22.2%

6. Varieties of Encephalopathies (total n = 22)

Type	No. of Cases	Percentage
Toxic	8	36.4%
Metabolic	4	18.2%
Vascular	6	27.3%
Infective	4	18.2%

7. Varieties of Leukoencephalopathies (total n = 14)

Class/ Entity	No. of Cases	Percentage
Canavan's Disease	4	28.6%
Metachromatic Leukodystrophy	3	21.4%
Van Der Knapp's Disease	2	14.3%
Progressive Multifocal Leukoencephalopathy	4	28.6%
Mitochondrial Leukoencephalopathy	1	7.1%

V. Result: -

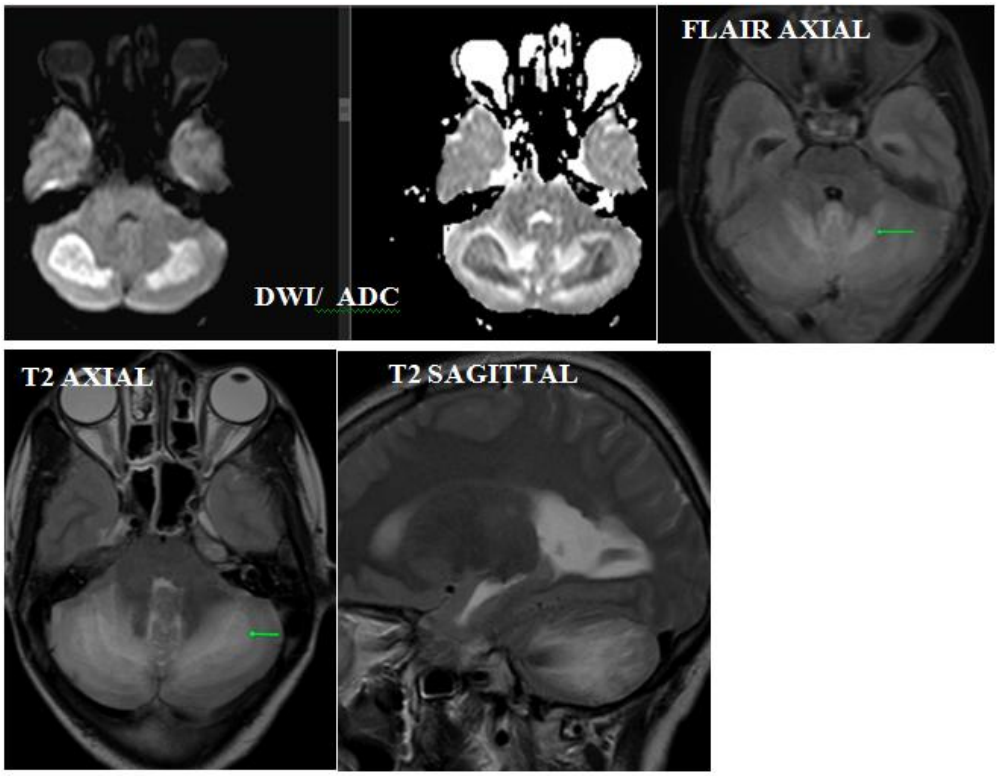
The majority of the 36 patients were females (n=20) and age wise most affected were paediatric patients (0-18 years old). The most common clinical presentation was altered sensorium which was closely followed by fever. Seizures and delayed milestones were equally present. The deep gray matter/ deep nuclei were the commonest(38.7%) site of involvement followed by the white matter (22.4%). In addition, many cases of white matter disease were further confirmed by MR spectroscopy (n=09).

VI. Discussion: -

1. Toxic Encephalopathy

Case 1.24yr old female with complaints of acute gastroenteritis since 14 days, on USG liver abscess in right lobe of liver. Sudden onset of gait abnormality, ataxia and chorea.

MRI suggests diffuse bilaterally symmetrical T2/FLAIR hyperintensity areas involving bilateral cerebellar hemispheres and dentate nuclei.
DWI/ADC sequences showed corresponding areas of diffusion restriction.

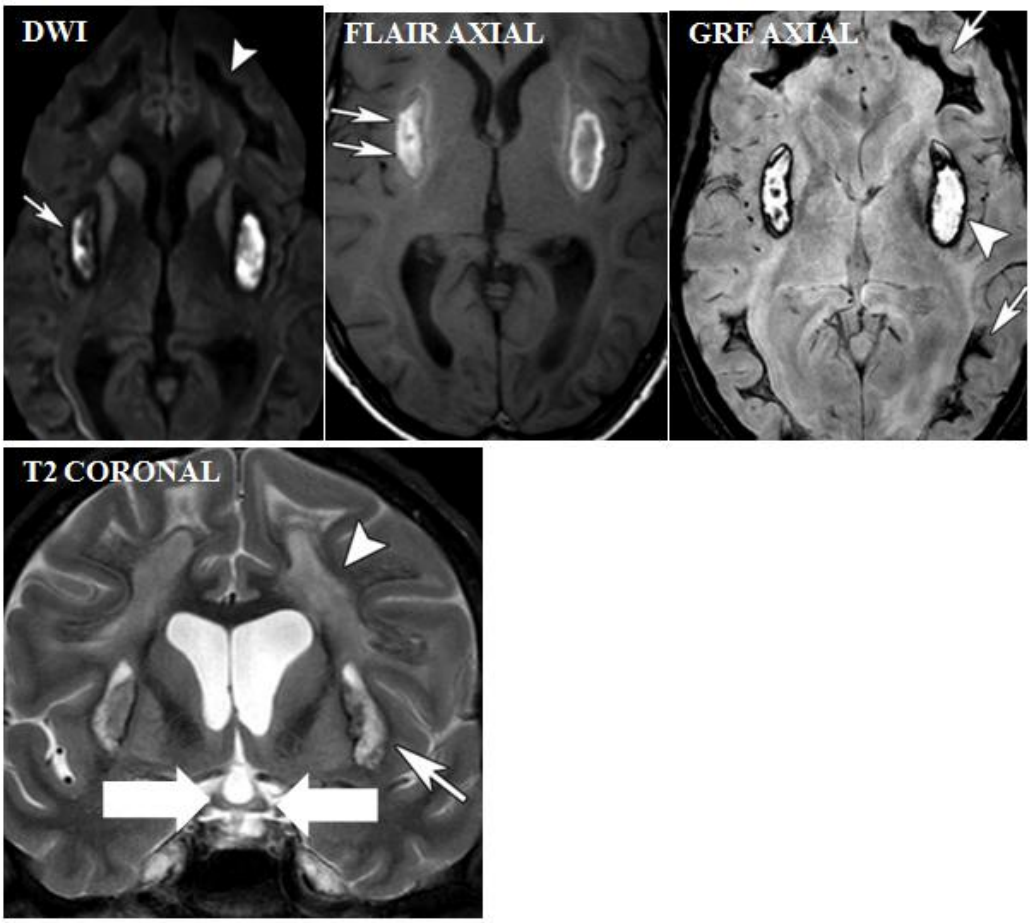


A. Metronidazole-induced Brain Toxicity

Metronidazole is an antibiotic that is used to treat a wide variety of bacterial and protozoal infections and was recently reported to rarely cause CNS toxic effects.These toxic effects can affect patients of all ages, usually appearing during prolonged treatment, frequently over 25 days of use (mean duration, 54 days), but it is important to emphasize that shorter periods, such as 7 days, have also been described to cause such toxic effects [(19,20)]. In nearly all cases of metronidazole-induced brain toxicity (up to 93%), MR images showbilateral symmetric lesions in the cerebellum, particularly involving the dentate nuclei. A majority of cases (86%) show a characteristic pattern of bilateral symmetric involvement of the dentate nuclei, vestibular nuclei, tegmentum, and superior olivary nuclei. A lack of enhanced lesions with T2-weighted and FLAIR hyperintensity is the most common finding.

Case 2. A 36year old male patient had acute-hyperacute (2-3 days) history of severe gastroenteritis with sudden loss of vision of left eye and dimunition of vision in right eye. Patient has history of recent consumption of country liquor 3 and 4 days ago.

On MRI, there is bilateral symmetrical T1/T2/FLAIR hyperintensity in bilateral basal ganglia (predominantly involving putamen and relative globus pallidus sparing) and bilateral optic chiasma. These areas show diffusion restriction on DWI/ADC sequences. On Gradient (GRE/SWI) sequences there is blooming in bilateral basal ganglia and also large confluent areas of blooming in bilateral fronto-parietal white matter.



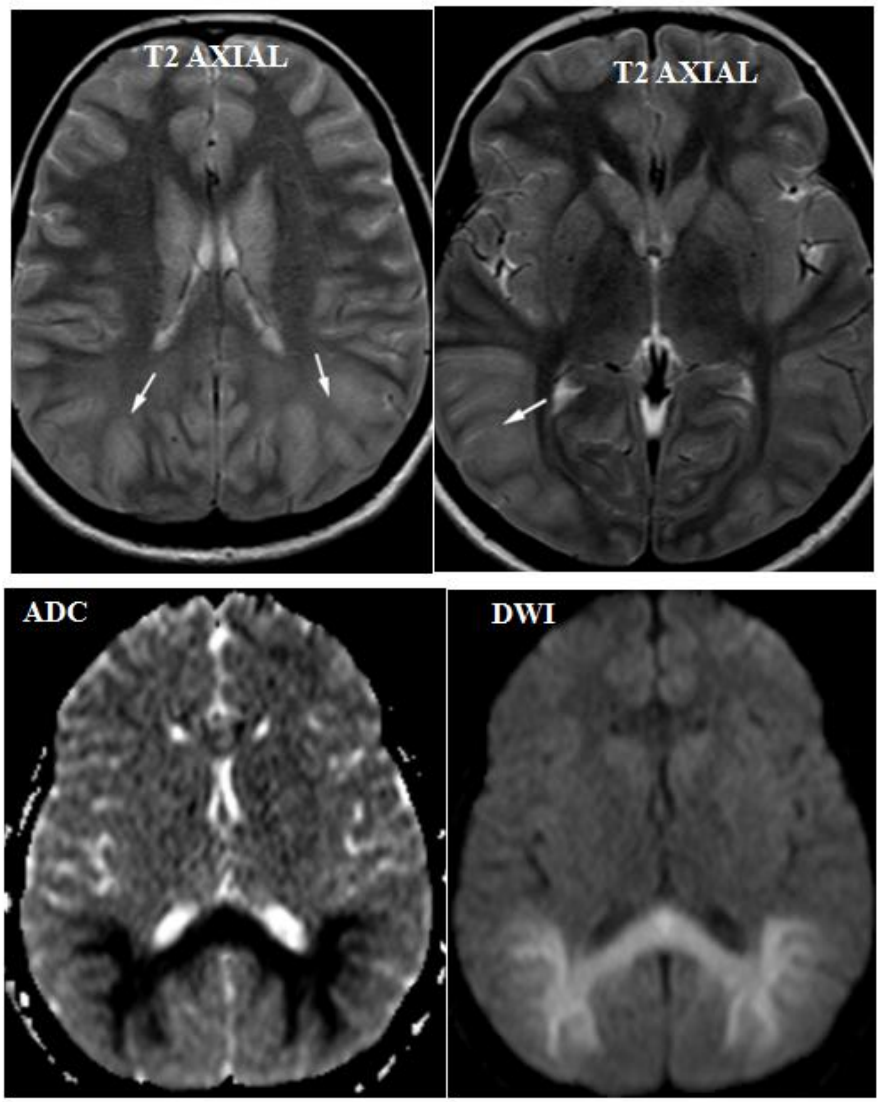
B. Methanol Induced Toxicity

Methanol is a strong CNS depressant and a common component in solvents, perfumes, paint removers, and gasoline mixtures. Methanol causes severe metabolic acidosis, with patients commonly presenting in a comatose state after preceding visual and gastrointestinal symptoms. Imaging can play an important role in making this diagnosis [21,22,23,24].Bilateral symmetric basal ganglia necrosis is the most characteristic imaging feature of methanol poisoning. Selective or predominant involvement of the putamina with relative sparing of the globus pallidus is suggestive of methanol poisoning. Hemorrhagic necrosis appears as an area of hyperattenuation on CT images. MR images show T2-weighted and FLAIR hyperintensity, and susceptibility-weighted imaging sequences sometimes show associated changes owing to the presence of hemorrhage. Restricted diffusion is depicted in the acute phases, and MR spectroscopy shows reduced N-acetylaspartate and elevated lactate peaks[21,22,23,24].

2. Metabolic Encephalopathy

Case 1.A 42 year old female patient present with complains of altered sensorium, few (3-4) episodes of seizures and sudden loss of consciousness. Patient is a known case of Type II uncontrolled diabetes with 3 antihyperglycemic drugs and insulin injection twice daily.

On MRI, there is diffuse T2 hyperintensity noted involving bilateral parieto-temporal region and splenium of corpus callosum. There is strong area of diffusion restriction in corresponding region in bilateral symmetrical parieto-temporal cortex and also involves splenium of corpus callosum.



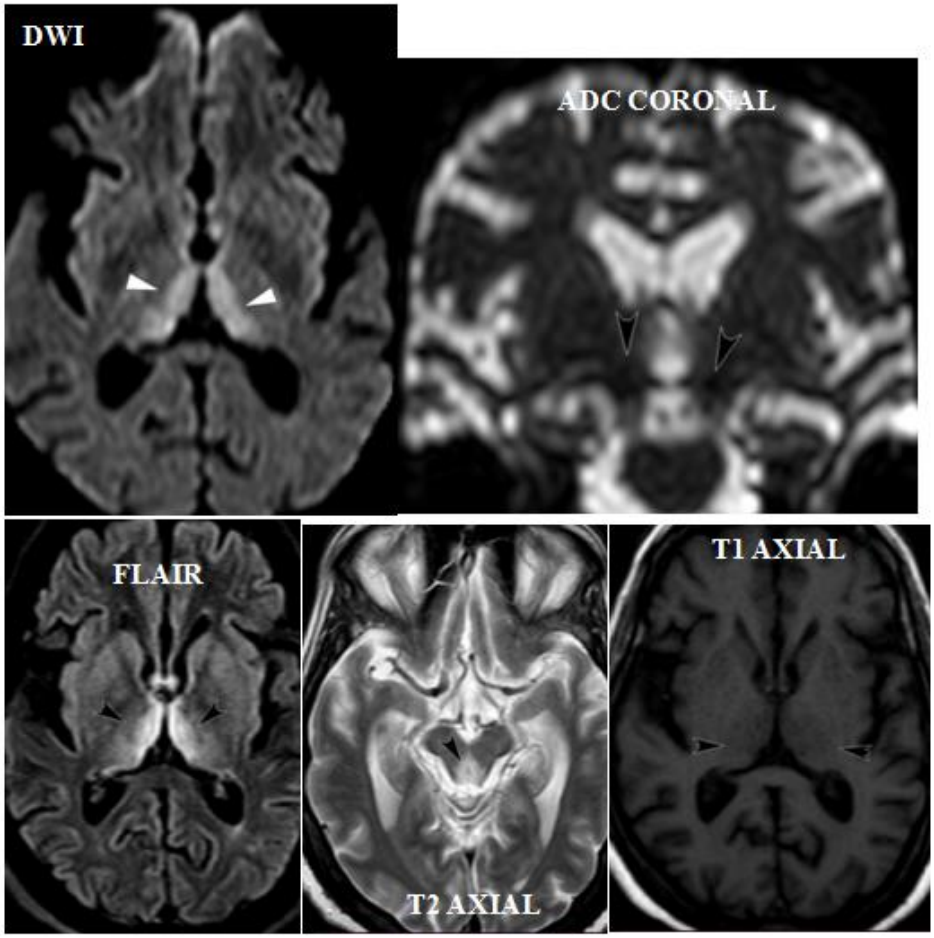
A. Hypoglycemic Encephalopathy

Adult hypoglycemic encephalopathy or hypoglycemic brain injury is caused by an imbalance between supply and use of glucose by cerebral cells, leading to brain injury [25].The clinical manifestation is characterized by seizures, a depressed level of consciousness, and even coma in patients with diabetes (commonly in those patients undergoing insulin replacement therapy) [21,25].

Hypoglycemic encephalopathy has a predilection for posterior and deep regions. The most common imaging findings are symmetric hyperintensities on T2-weighted and FLAIR images and strong restricted diffusion affecting the parieto-occipital and temporal regions on diffusion-weighted images. Another suggestive characteristic finding is the sparing of the thalamiand cerebellum. In newborns, the most common cause is maternal diabetes, which usually manifests in the first 3 postnatal days. The most characteristic pattern of neonatal hypoglycemia is symmetric posterior parieto-occipital gray and white matter signal abnormality with diffusion restriction involving the optic radiations and frequently the posterior thalami [21,26].

Case 2.A 37 year old male chronic alcoholic patient presented with complaint of ophthalmoplegia and confusion with altered sensorium. The family gives history of improper feeding habits.

On MRI, there is diffuse T2/FLAIR hyperintensity, corresponding T1 hypointensityand restricted diffusion noted involving periaqueductal region and bilateral medial thalamus.



B. Wernicke's Encephalopathy(WE)

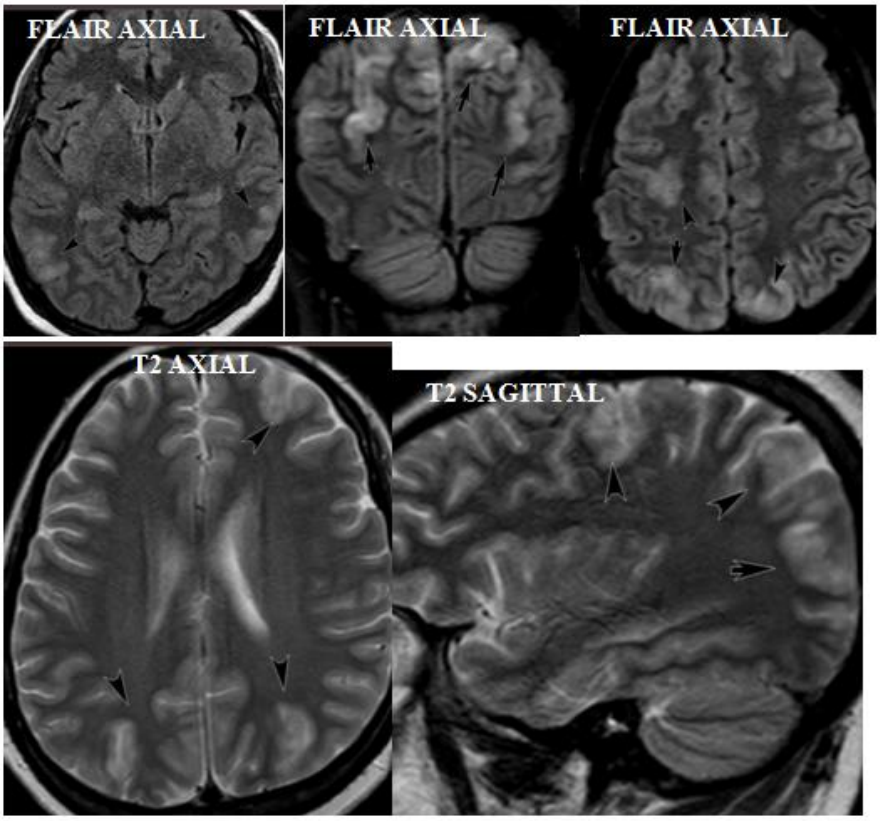
Wernicke's encephalopathy is usually related to chronic and frequent alcohol intake. The underlying pathophysiology is associated with nutritional deficiencies, notably thiamine (vitamin B1). Thiamine is important in maintaining osmotic gradients across the cell membrane, ensuring its integrity [(21)]. Other important causes of wernicke's encephalopathy include hyperemesis (pregnancyrelated, chemotherapy), eating disorders, and bariatric surgery, any of which can lead to secondary malnutrition [(21,27,28)]. The classic clinical triad of symptoms, including ocular dysfunction (nystagmus, ophthalmoplegia), ataxia, and confusion, manifests in only 30% of patients [(28)].

Imaging plays an important role in early wernicke's encephalopathy diagnosis. MRI is much more sensitive than CT. During the acute phase, symmetric bilateral T2-weighted and FLAIR hyperintensities and restricted diffusion can be observed in affected areas. Common sites involved in wernicke's encephalopathy include the regions surrounding the third ventricle (the medial thalami in 85% of cases, the mammillary bodies in 60% of cases, and the hypothalamus), the tectal plate and the periaqueductal gray matter in two-thirds of cases, and the putamina[(21,27,28)]. Strong uniform postcontrast enhancement of the mammillary bodies is observed in up to 80% of cases and is considered a pathognomonic finding for wernicke's encephalopathy.

3. Vascular Encephalopathy

Case 1.A 25 year old female was admitted prophylactically for diagnosis of pregnancy induced hypertension. The patient had an 2 episodes of seizures on 3rd day with post seizure persistent headache. Although post convulsion patient was immediately taken for emergency LSCS, post operation patient had another 2 episodes of convulsion.

On MRI, multiple patchy T2/FLAIR hyperintense areas without diffusion restriction noted in cortical and subcortical areas of bilateral high fronto-parietal region , bilateral posterior temporal and occipital regions and also noted in posterior part of right capsuloganglionic region.



A. Posterior Reversible Encephalopathy Syndrome (PRES)

PRES, also known as reversible posterior leukoencephalopathy syndrome, refers to a clinic-radiologic disorder of potentially reversible subcortical vasogenic brain edema in patients with classic acute neurologic symptoms (seizure in 60%–75%, altered mental function and headache in 20%–25%) in the setting of several conditions, such as hypertension, preeclampsia, renal failure, sepsis, thrombocytopenia.PRES was classically described as a cerebrovascular autoregulatory disorder caused by hypertension. Theories have a similar shared mechanism, advocating endothelial injury and dysfunction secondary to different causes (cytotoxic, immunogenic), ultimately resulting in vasogenic edema. Interstitial fluid accumulates in the subcortical white matter, with a predilection for the parietal and occipital lobes [21,29,30].

Imaging findings include changes associatedwith vasogenic edema, commonly bilateral and asymmetric high signal intensity on T2-weighted and FLAIR images and hypoattenuation on CT images. Diffusion-weighted images and apparent diffusion coefficient maps are often negative. There are many patterns of cerebral involvement thathave been described, including

(a) parietooccipital involvement, the most common and suggestive pattern (up to 90%, also known as classic PRES);

(b) the superior frontal sulcus pattern (70%);

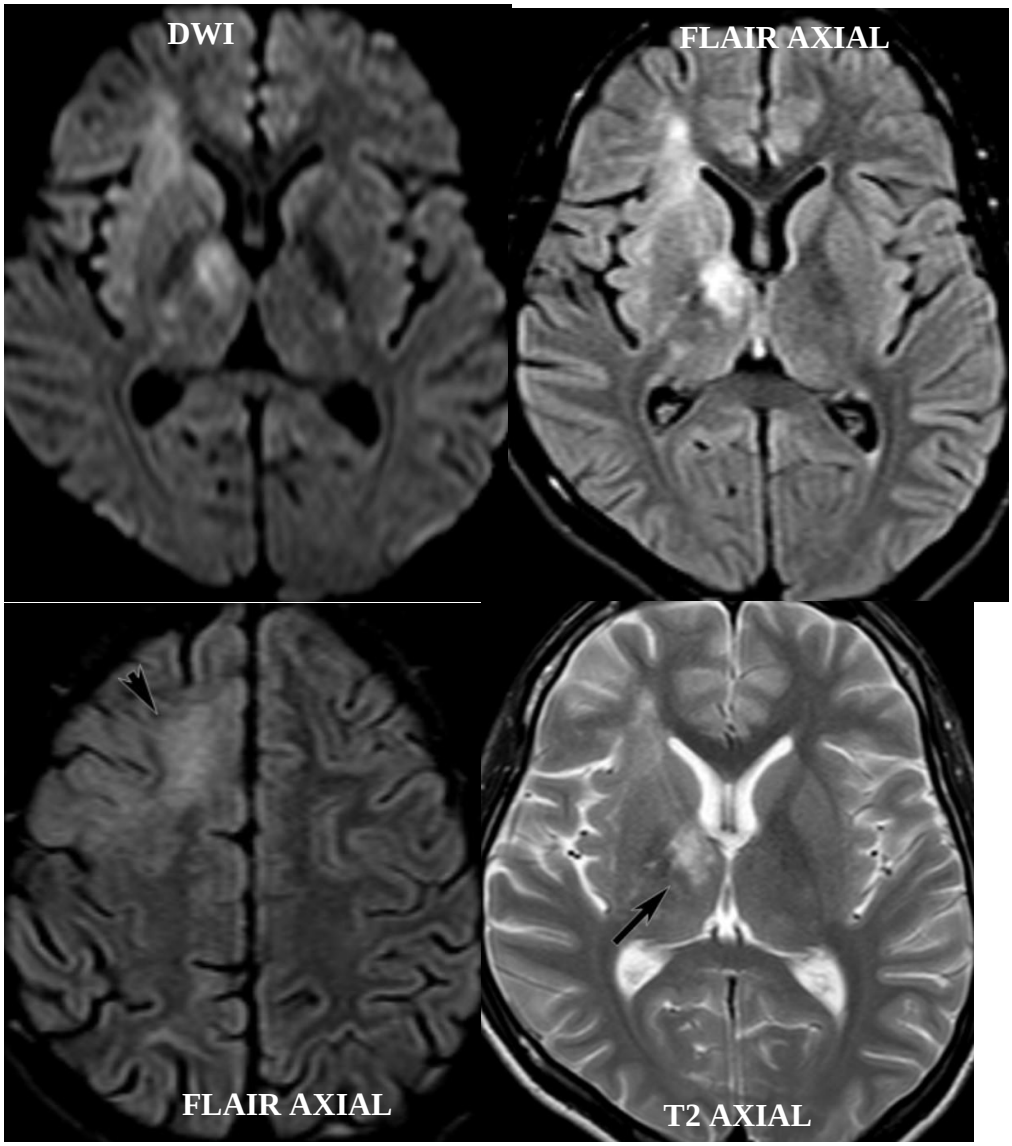
(c) the holohemispheric watershed pattern (50%); and

(d) involvement in other less common sites, such as the cerebellum, basal ganglia, and brainstem.

4. Infective Encephalopathy

Case 1.A 46year old HIV reactive male patient presented with complaints of gait ataxia and progressive loss of cognitive function over a period of 2 months. The person is also on anti-psychotics for behavioural dysfunction for a clinical diagnosis of schizophrenia.

On MRI, there is diffuse T2/FLAIR hyperintensity noted in bilateral frontal (right>left) subcortical region and also involves right thalamo-capsulo-ganglionic region. There is corresponding diffusion restriction in bilateral high fronto-parietal region.



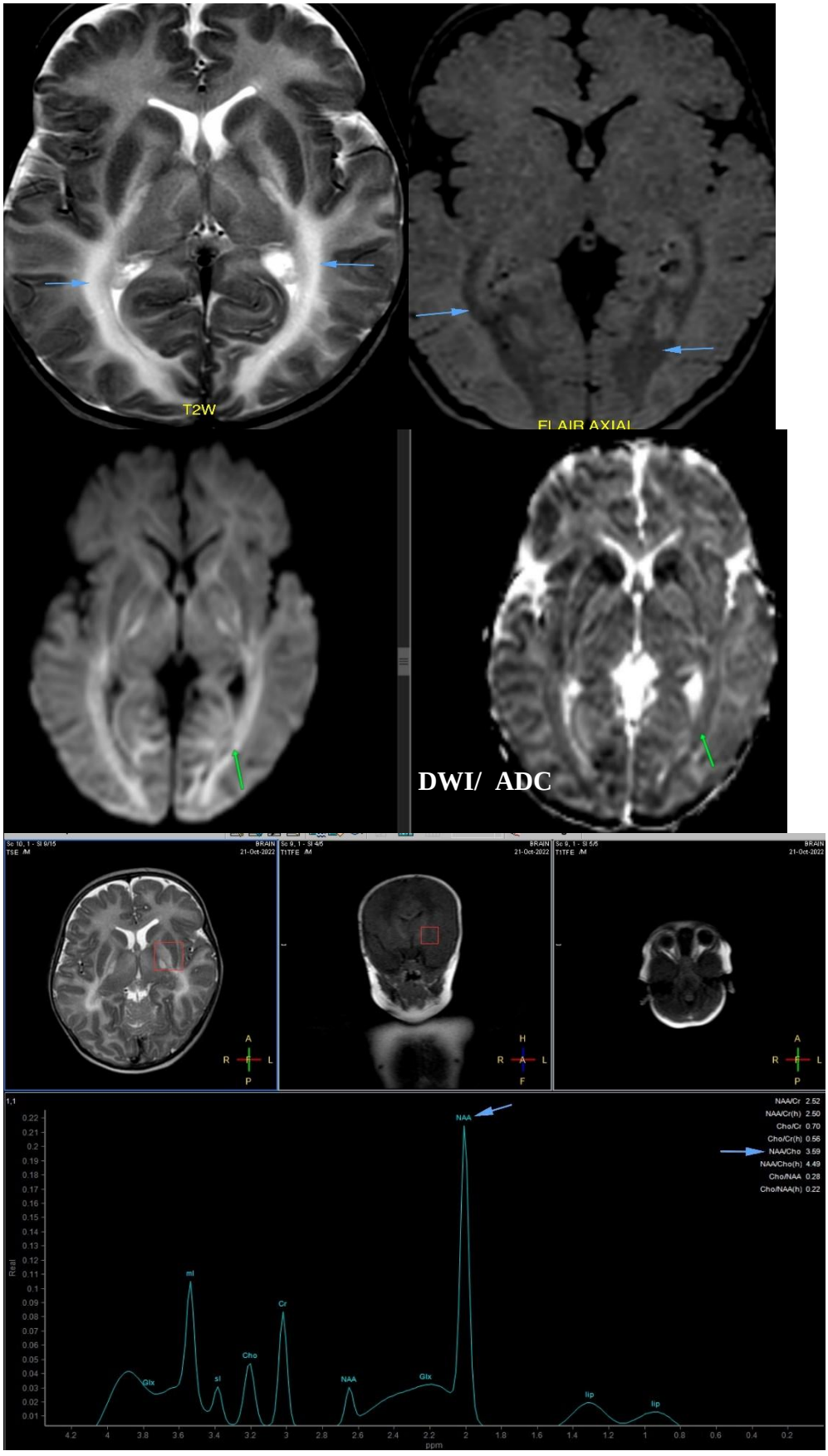
A. HIV Encephalopathy

HIV encephalopathy, also referred to as HIV-associated neurological disorder (HAND), includes a range of neurocognitive defects of varying severity following HIV infection. The clinical presentation of this condition varies from asymptomatic or minor neurocognitive impairment to severe dementia. A low CD4 count and high plasma viral load are the key factors determining the development of HIV encephalitis. There has been a significant decrease in the severity of HIV encephalitis over the years, owing to the advent and widespread usage of antiretroviral therapy (ART)[(31)]. Neuroimaging studies in patients suffering from HIV encephalopathy usually show cerebral atrophy on CT or MRI. In advanced stages of the disease, on T2-weighted sequences, multiple symmetric foci of hyperintense, non-enhancing lesions are seen predominantly in a subcortical distribution[(32)].

5. Congenital and Adult Leukoencephalopathies

Case 1.1 year old boy, born to a non-consanguineous couple, at term after uneventful pregnancy and delivery, presented with complaints of progressive difficulty in walking, decreased oral acceptance and multiple episodes of seizures.

On MRI, Prominent T2 hyperintense and T1/FLAIR hypointense signal involving deep and subcortical white matter along with U fibres bilaterally. On DWI sequences there is marked diffusion restriction entire white matter which was predominant in posterior forceps/ forceps major. Consequent MR Spectropscopy showed elevated NAA peak with relative reduction in peaks of choline and creatine.

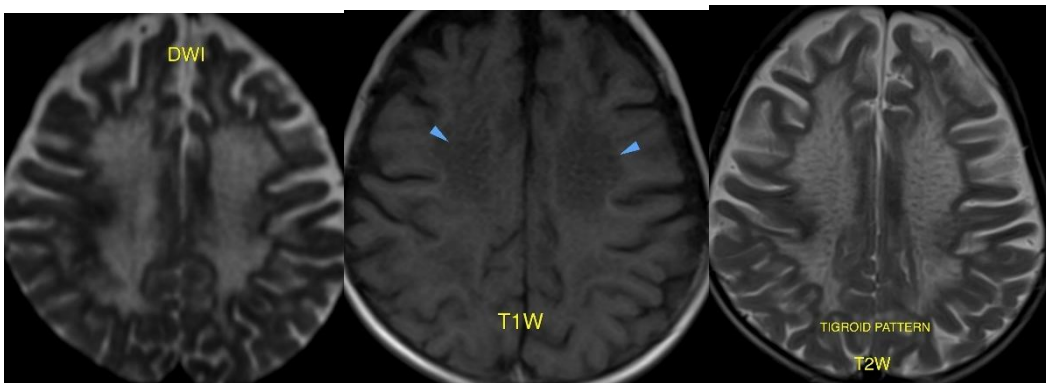

T2W
FLAIR AXIAL
DWI/ ADC
NAA
Cr
Cho
mI
Glx
NAA/Cr 2.52
NAA/Cr(h) 2.50
Cho/Cr 0.70
Cho/Cr(h) 0.56
NAA/Cho 3.59
NAA/Cho(h) 4.49
Cho/NAA 0.28
Cho/NAA(h) 0.22

A. Canavan's Disease

Canavan disease, also called as spongiform degeneration of cerebral white matter, is an autosomal recessive demyelinating disease caused by mutations in the aspartoacylase (*ASPA)* gene located in the short arm of chromosome 17, resulting in the deficiency of aspartoacyclase, which catalyzes the breakdown of NAA; excessive accumulation of NAA is responsible for the central nervous system changes in this disease.[33] Canavan disease demonstrates bilateral symmetric T2 white matter hyperintensity, including involvement of the subcortical arcuate fibers. The involvement is diffuse throughout the cerebral white matter, does not show enhancement on computed tomography (CT) or MR imaging, and demonstrates variable involvement of the basal ganglia and cerebellar white matter.[34]Canavan's disease is diagnosis is established by elevated NAA signal in MR spectroscopy conjunction with absence of myelination and progressive increase in head circumference.

Case 2.2 and half year old female patient with developmental delay and generalized rigidity since the age of 18 months and retarded neuropsychomotor development. She had no specific birth history and showed normal pattern of development until the onset of symptoms. There was regression of developmental milestones with continuous worsening.

On MRI, diffuse confluent multifocal T2 hyperintensity with interspersed hypointense bands/ prominent lateral Virchow robin spaces (tigroid appearance) predominantly in periventricular white matter with relative sparing of subcortical white matter. No evidence of significant diffusion restriction noted.

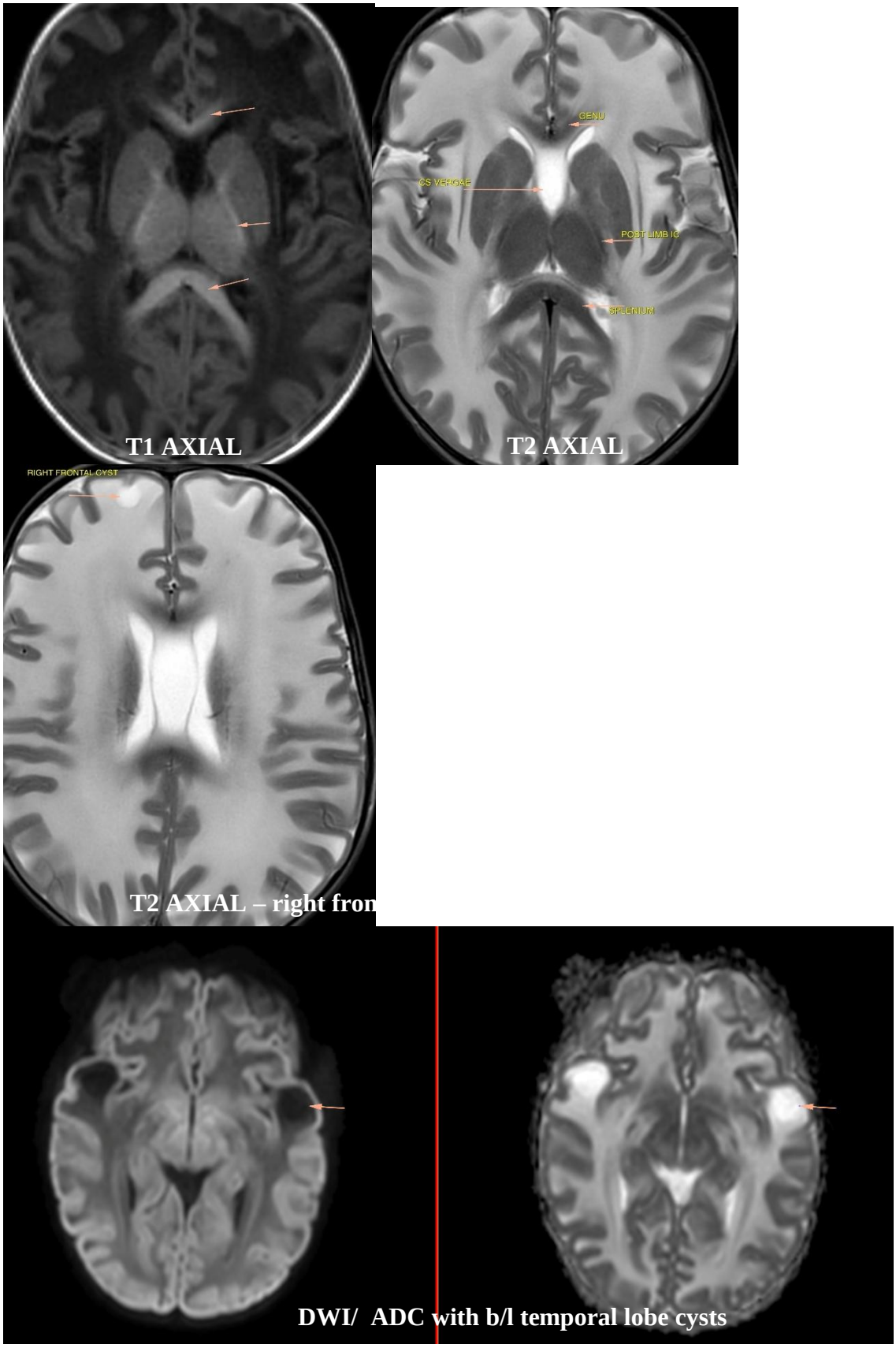


B. Metachromatic Leukodystrophy

Metachromatic leukodystrophy is an autosomal recessive lysosomal condition due to arylsulfatase A (ARSA) gene mutations, resulting in deficiency of the enzyme arylsulfatase A (ASA) that leads to accumulation of 3-O-sulfogalactosylceramide (sulfatide) in oligodendrocytes, Schwann cells, and some neurons [35,36].The initial symptoms are often behavioral and psychiatric changes, followed by a slow decline in memory and intellectual abilities. Later, the onset of motor symptoms including spastic paraparesis and cerebellar ataxia and peripheral neuropathy occur.MRI findings consist of confluent, symmetricT2 hyperintensity in the frontal or periventricular white matter. The subcortical U fibers are spared, and frequently some frontal predominance is present in patients with adult-onset metachromatic leukodystrophy. Loss of white matter volume results in brain atrophy in the late stages of the disease [42,43].

Case 3.A 2 year old male child presented with relative macrocephaly with delayed milestones predominantly motor and recurrent seizures. No specific epileptic syndrome was diagnosed. Mild spasticity noted involving limbs.

On MRI, there is relative megalencephaly with extensive dysmyelination resultant swollen appearance of the cerebral white matter defined by diffuse, widened, bilateral, and symmetric T2-weighted hyperintensity and T1-weighted hypointensity of cerebral white matter. Bilateral subcortical cysts of CSF intensity affecting the anterior temporal regions and right frontal lobes which may increase in size due to further cerebral atrophy.



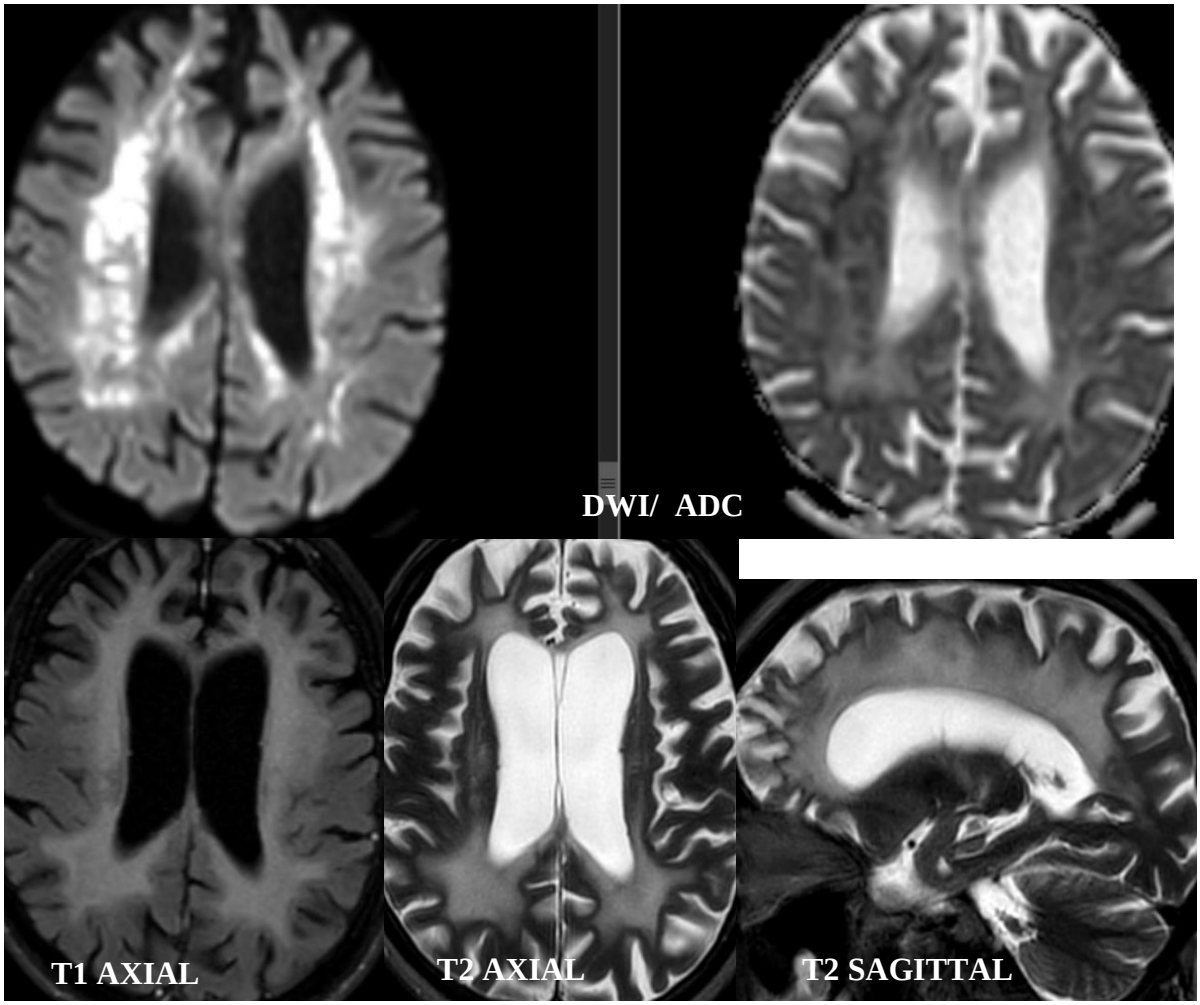
C. Van Der Knapp Disease/ Megalencephalic leukoencephalopathy with Subcortical Cysts

Van der Knaap disease, also known as megalencephalic leukoencephalopathy with subcortical cysts (MLC), is a rare autosomal disorder, with no exact prevalence but more than 150 cases were reported in the literature. It was

more prevalent in some ethnicities where consanguinity is common.[37] Patients with this disease suffer from neurodegenerative features which include mild gross motor developmental delay, gradual onset of ataxia, spasticity, dysarthria, dystonia, and sometimes extrapyramidal findings**.** MRI findings include:[38]

- Megalencephaly
- Expanded cerebral white matter defined by diffuse, bilateral, and symmetric T2-weighted hyperintensity and T1-weighted hypointensity of cerebral white matter
- Bilateral subcortical cysts of CSF intensity affecting the anterior temporal regions and frontoparietal lobes which may increase in size due to further cerebral atrophy
- Abnormal diffusion signal on diffusion-weighted magnetic resonance imaging (DWI), but mild in the cerebellar white matter
- Sparing of the deep and cerebellar white matter.

Case 4. A 49 year old male patient with HIV reactive clinical status presented with gait ataxia, seizures and finally altered sensorium. Post admission on evaluation there was diplopia in right eye field.
On MRI, multifocal, confluent asymmetric periventricular white matter and subcortical U-fiber involvement with a predilection for the parieto-occipital regions. The lesion showpatchy but marked diffusion restriction. There is little or no mass effect or post contrast enhancement.



D. Progressive Multifocal Leukoencephaloapthy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the central nervous system caused by the reactivation of John Cunningham virus (JCV) in immunocompromised patients, most commonly in human immunodeficiency virus (HIV) infection, and less commonly in those receiving various immunosuppressive regimens. The characteristic histological features are foci of demyelination rimmed by inclusion bearing oligodendrocytes and bizarre astrocytes of variable morphology. MRI is the imaging modality of choice, with greater sensitivity than CT [39,40] and shows multifocal asymmetric, white matter lesions, hyper-intense on T2 weighted images and hypo-intense on T1 weighted images. These lesions mostly do not enhance

on contrast The lesions are often bilateral, rarely can be unilateral. [39,40] The lesion location is periventricular and at the gray white interface, involving the U fibers thus giving a scalloped appearance. The parieto-occipital and frontal locations are most common and approximately one third of cases have some involvement of the posterior fossa, though other lobes may also be involved. Isolated infratentorial involvement is found in about 10% of cases. [41]

VII. Conclusion: -

Comparative image analysis of different identically angulated MRI sequences including DWI and T2* WI or SWI is a prerequisite for the reliable differential diagnostic assessment of white matter lesions.

Characteristic lesion patterns can be identified, taking into account the architecture and vascular supply of the white matter. The etiology of white matter lesions includes vascular, inflammatory, metabolic and neoplastic processes.

Vascular pathologies are in the foreground, especially in the elderly; age-associated arteriosclerosis with typical risk factors and CAA account for over 90% of microangiopathies.

Involvement of U-fibers or the cortex is more often found in inflammatory or metabolic causes, although the latter are rare in adulthood.

MR Spectroscopy complementary to conventional MRI proved to be a valuable tool to establish the diagnosis of leukodystrophies.

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