
Acute leucoencephalopathy with restriction of diffusion-a case report

Vivek Singh, Vaishali Tomar, Alok Kumar, Rajendra V. Phadke*

Department of Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Abstract. Acute white matter insult in a non traumatic, non ischemic background has been recently identified in certain clinical situations. Named toxic leucoencephalopathy, it may be caused by exposure to a wide variety of agents, including cranial irradiation, therapeutic agents, drugs of abuse, and environmental toxins. Extensive central white matter restriction of diffusion in the absence of significant T2 or Fluid-attenuated inversion recovery (FLAIR) abnormality is the imaging hallmark on Magnetic Resonance Imaging (MRI). Reversibility of the symptoms after the withdrawal of toxin has been shown in a few reports. We present one such case with reversal of changes on MRI and clinical improvement.

Key words: ADEM, intramyelinic edema, PRES, toxic leucoencephalopathy

1. Introduction

Leucoencephalopathy is a structural alteration of cerebral white matter in which myelin suffers the most damage (1). Toxic leucoencephalopathy is a recently identified entity seen in patients exposed to a wide variety of agents like cranial irradiation, therapeutic agents, drugs of abuse and environmental toxins (1). Prevalence of toxic leucoencephalopathy is not known. The syndrome is increasingly being recognized among patients in whom neurobehavioral disturbances develop after exposure to endogenous or exogenous toxins.

Use of magnetic resonance imaging (MRI), especially the diffusion weighted imaging (DWI) has led to a greater appreciation of the damage that leukotoxic agents can inflict on white matter (2). We present a case of symmetric posterior supratentorial leucoencephalopathy in which exact toxin could not be identified but the reversibility is well depicted.

2. Case report

A 7 year-old male child presented elsewhere with a short history of mild fever and had two episodes of vomiting. He received multiple medications including antibiotics empirically. He went into altered sensorium on the 3rd day. There was no history of seizures or past history of any illness. There was no history of lymphadenopathy or any skin rashes. On examination there was tachycardia (126 beats/min) and mild hypotension (BP 90/60 mm of Hg) but there were no signs of dehydration. The patient was afebrile. Examination of the nervous system revealed altered sensorium. Muscle tone was decreased in all four limbs and plantar reflexes showed extensor response bilaterally. Laboratory tests were normal except raised total leukocyte count (32000/microlit). Peripheral smear for malarial parasite was negative and markers for viral infection were negative. Bone marrow and CSF examination were normal.

Brain MRI performed during the acute episode revealed significant symmetrical diffusion restriction (Figure 1C), with reduced apparent diffusion coefficient (ADC) values in the parietal white matter bilaterally extending partly to the posterior frontal region. The ADC values were in the range of 293 – 380 cm⁻⁶ /sec² in the involved white matter (Figure 1D), compared to 800 - 950 cm⁻⁶/sec² in the unaffected white matter. Fluid-attenuated inversion recovery (FLAIR) images

*Correspondence: Dr. Rajendra V. Phadke, M.D.
Professor and head, Department of Radiodiagnosis,
Sanjay Gandhi Post Graduate Institute of Medical Sciences,
Lucknow, UP, 226014- India
E-mail : rphadke@sgpgi.ac.in
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(Figure 1B) showed only subtle signal changes with no signal changes in T2W images (Figure 1A). No abnormal enhancement on post contrast scan was seen.

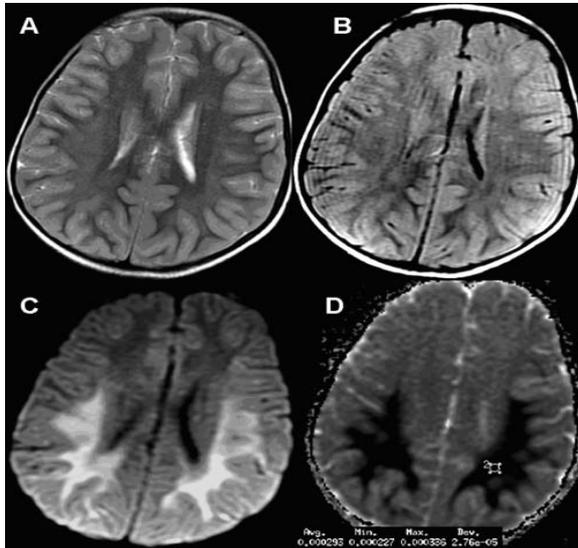


Fig. 1. MRI shows no abnormality on T2W image (A) with subtle changes in FLAIR (B), DWI (at b value 1000 sec/mm²) shows hyperintensity (C) with restriction on ADC map- average value 293 cm⁶/sec² (D).

There was complete resolution in DWI changes in the follow-up MRI after 13 days (Figures 2C and D) and the T2 and FLAIR images (Figures 2A and B) did not show any residual change in the affected region. Clinically complete resolution was seen on follow up after one month.

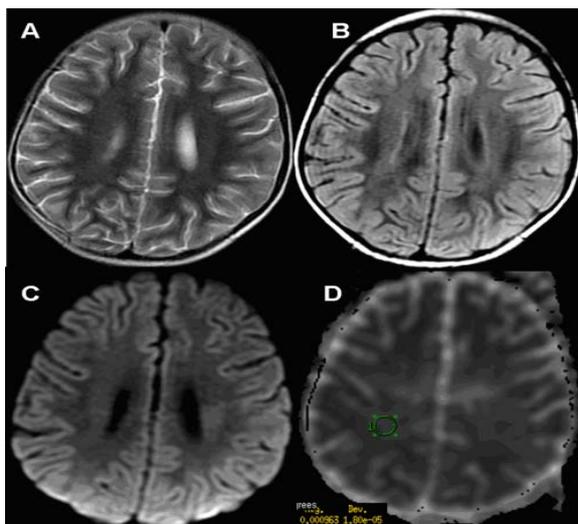


Fig. 2. Follow up MRI performed after 13 days shows no abnormality in T2W (A), FLAIR (B), DWI (C) and ADC map shows no restriction average value 963 cm⁶/sec² (D).

3. Discussion

Diffusion-weighted (DW) magnetic resonance (MR) imaging provides potentially unique information on the viability of brain tissue. It provides image contrast that is dependent on the molecular motion of water, which may be substantially altered by disease.

Both DWI and the corresponding apparent diffusion coefficient (ADC) maps have to be studied to identify areas with restricted diffusion. In the brain, apparent diffusion is not isotropic (the same in all directions); it is anisotropic (varies in different directions), particularly in white matter. The cause of the anisotropic nature of white matter is not completely understood, but increasing anisotropy has also been noted in the developing brain before T1- and T2-weighted imaging or histologic evidence of myelination becomes evident (3,4). It is likely that in addition to axonal direction and myelination, other physiologic processes, such as axolemmic flow, extracellular bulk flow, capillary blood flow, and intracellular streaming, may contribute to white matter anisotropy (5).

Increased cell turgidity or increased cellularity of a lesion with reduction of extracellular fluid space leads to restricted diffusion as apparent on DWI. Of these, increased cell turgidity often due to cytotoxic edema has the most important implications in terms of cell viability.

Restricted diffusion associated with acute ischemia comes 30 minutes after an ischemic insult. The ADC continues to decrease and is most reduced at 8–32 hours. The ADC remains markedly reduced for 3–5 days. The ADC values measured at these times are approximately 16%–68% below those of normal tissue. The ADC returns to baseline at 1–4 weeks. With early reperfusion, pseudonormalization (return to baseline of the ADC reduction associated with acute ischemic stroke) may occur at a much earlier time—as early as 1–2 days. However while pseudonormalization of ADC may occur in due course, the FLAIR and T2 images show the ischemic tissue damage subsequently.

Restricted diffusion is seen in ischemia/infarction and encephalitis. Posterior reversible encephalopathy (PRES) and acute disseminated encephalomyelitis (ADEM) may show focal restriction of diffusion in some cases. ADEM and PRES form the main differential diagnosis in a case like ours.

Acute disseminated encephalomyelitis lesions have ADCs higher than those of normal white matter, likely as a result of demyelination and increased extracellular water. In ADEM there are

Multifocal lesions with T2 abnormality that are best seen in FLAIR and they are moderate to large usually asymmetric patchy areas involving deep and subcortical white matter of cerebral and cerebellar hemisphere and brainstem. These may show hemorrhage (then known as acute hemorrhagic encephalomyelitis). The lesions usually exhibit mild mass effect and may show enhancement which may be nodular, patchy or gyriform.

Posterior reversible encephalopathy syndrome (PRES) is primarily described in acute systemic hypertension. The term describes a potentially reversible imaging appearance and symptomatology that is shared by a diverse array of causes, including hypertension, eclampsia and preeclampsia, immunosuppressive medications such as cyclosporine, various antineoplastic agents, severe hypercalcemia, thrombocytopenic syndromes, Henoch-Schönlein purpura, hemolytic uremic syndrome, amyloid angiopathy, systemic lupus erythematosus, and various causes of renal failure (6) and there are reports of other etiologies like porphyria and cerebral malaria etc. PRES is usually seen in parieto-occipital white matter symmetrically. In a study the most common DWI appearance was isointensity (54.7%) and DWI bright T2 shine-through (28%). Diffusion restriction occurred in a minority (17.3%) of patients; it was usually punctate and surrounded by much larger areas of edema (6).

Toxic leukoencephalopathy can occur in any age group and any patient care setting (1,2). No specific age group predilection is found and it may be caused by exposure to a wide variety of agents, including cranial irradiation, chemotherapy, immunosuppressive therapy, antimicrobial medications (e.g., metronidazole), environmental toxins (e.g., carbon monoxide), and drug abuse (1,2).

Toxic leukoencephalopathy involves particularly white-matter tracts devoted to higher cerebral function, causing clinical features that range from inattention, forgetfulness, and changes in personality to dementia, coma, and death (1,2). The neurological findings in acute toxic leukoencephalopathy can be reversed if promptly recognized and treated. Recent reports have highlighted the value of diffusion-weighted imaging (DWI) to document radiological reversal of findings in these patients (2,7). McKinney et al. (2) proposed to refer this entity as acute toxic leukoencephalopathy.

In our case patient had taken multiple drugs for pyrexia and vomiting before landing into altered sensorium. After withdrawal of all the

medications and with only supportive treatment and diet, the patient improved clinically as well as radiologically. The blood pressure was normal and the low ADC values are uncommon in PRES. The imaging also does not suggest ADEM and acute toxic leukoencephalopathy is the most likely radiological diagnosis.

Intramyelinic edema is implicated in the pathophysiology of acute toxic leukoencephalopathy (2). The pathophysiology may be akin to transient DWI restricted lesions of splenium of corpus callosum seen in varied etiologies (8). These reversible lesions have been attributed to excitotoxic mechanisms (9). Excitotoxic edema has been considered to be intramyelinic at least in early phase of the injury due to separation of the myelin layers and edema in the intramyelinic clefts (8). This explains why this type of edema is reversible in many cases. Intramyelinic edema is associated with a reduction in the ADC, but it does not imply neuronal damage. Therefore this type of edema is usually transitory and DWI abnormalities normalize with time or following removal of causative pathological factor (8,9).

Diffusion restrictions in grey matter were seen more often than not signifies irreversible damage and cell death. There are very few reports showing reversibility of diffusion changes or tissue survival in grey matter with early revascularization (10). The scenario is somewhat different in white matter. White matter fibre tract arrangement uniquely affects diffusion. Predominant diffusion in white matter is in the direction of the axons and in turn in the direction of the tracts. Theoretically myelin sheath edema may be responsible for compression and temporary mechanical compromise of the axonal lumen and thereby restricting diffusion in axonal direction. Any restriction of diffusion in the axonal direction automatically presents as restricted diffusion since the diffusion in other directions is already low in white matter. If the pathological process resolves in time without damage to the axons, a good clinical and radiological recovery is expected as seen in these cases. The reversibility of changes in white matter is attributed to the limited injury caused through excitotoxic mechanism (9).

Thus, the brunt of the insult is taken by the glial cells and myelin sheath preserving the axons from irreversible damage. It is however not clear whether cytotoxic edema of the glial cells and myelin sheath cells (oligodendrocytes) alone is responsible for the restricted diffusion seen in these lesions or in combination with secondary

interruption of diffusion in axons. Reversibility of functional loss in these cases suggests that there may be a significant component of the latter.

Thus, the cause of reversible restriction of diffusion in toxic encephalopathy is not exactly known, but is presumably due to either intramyelinic edema (myelin vacuolation), cytotoxicity due to endothelial damage, or direct toxic demyelination. The reversibility of the DWI changes is best explained with intramyelinic edema theory (2).

4. Conclusion

Acute toxic leukoencephalopathy with restricted diffusion is a distinct entity easily differentiated from ADEM or PRES. The symmetrically distributed diffusion restriction in these white matter lesions may look alarming but is likely to have less severe implications in terms of tissue damage. Significant clinical and radiological improvement is often seen. Alerting the clinician to this potentially reversible syndrome can facilitate management.

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