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Research Article

NEURO-IMAGING IN "RASMUSSEN'S ENCEPHALITIS" *"CHRONIC FOCAL ENCEPHALITIS"*

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ABSTRACT
Rasmussen's Encephalitis (RE) is a rare, chronic inflammatory, progressive neuro-degenerative disease of brain of unknown origin, usually presenting as abrupt onset intractable seizure disorder in a previously normal child. The age group is usually between 2 to 10 years with peak incidence at 6 years (Oguni *et al.,* 1991). The seizures, typically, are focal motor type and lead to motor function deterioration, resulting in hemiparesis or hemiplegia as well as progressive cognitive decline. The seizures are usually drug-resistant (Rasmussen *et al.,* 1958; Bien *et al.,* 2005). Here, we present a Case of Rasmussen's Encephalitis with characteristic clinical and imaging findings- a seven years old male child who presented to the Department of Casualty with left-sided hemiparesis, deviation of angle of mouth to left side, high grade fever and seizures.

Keywords: *Chronic Focal Encephalitis, EPC-Epilepsia Partialis Continua, GTCS-Generalized Tonic Clonic Seizures, M.R.I. -Magnetic Resonance Imaging, RE-Rasmussen's Encephalitis*

INTRODUCTION
Rasmussen's Encephalitis (RE) is a rare, chronic, unihemispheric inflammatory neurodegenerative disease of brain affecting the children. It was first described by American neurologist Theodore Brown Rasmussen *et al.,* (1958). The diagnosis of Rasmussen's Encephalitis is based on clinical, imaging and histo-pathological findings. The seizures are usually focal, progressive and resistant to medication leading to neurological deficits. However, in the initial cases, the diagnosis is challenging. The etiology of this disease is still unclear. However, some scientists revealed cell-mediated immunity, precisely T-lymphocytes immune-reaction against the neurons and astrocytes (Bauer *et al.,* 2007; Schwab *et al.,* 2009). This hypothesis is further supported by study conducted by Granata *et al.,* (2011) which suggests that cytotoxic T-cells may be directed against the viral protein present in neurons and astrocytes (Granata *et al.,* 2011). But there is another school of thought that postulated the role of auto-immune pathology. Rogers *et al.,* (1994) found the role of anti-bodies against Glutamate receptors (GluR3). Some studies have also shown the association of RE with the viruses like Herpes simplex, CMV and EBV (Rogers *et al.,* 1994). There are no bio-markers for the diagnosis of RE. However, the presence of anti-GluR3 has some prognostic value as it cannot differentiate between RE and other non-inflammatory pathologies (Mantegazza *et al.,* 2002). Biopsy, however, provides important findings to diagnose RE as multifocal changes of the T-cell dominated encephalitis with activated microglia and reactive gliosis (Pardo *et al.,* 2004). Routine CSF examination has no role in diagnosis of RE (Bien *et al.,* 2005).
Magnetic Resonance Imaging (MRI) is the Preferred Neuro-imaging Modality for the Establishment of Diagnosis and Assessing the Type of Lesion

CASES
A seven years old male child presented to the Department of Casualty, Mahatma Gandhi Medical College and Hospital, Jaipur (Rajasthan) with the Complaints of generalized tonic-clonic seizures since 1 day, associated with deviation of angle of mouth to the left side and high grade fever. The patient gave history of several such episodes in past (8-10 episodes every month), with each episode lasting for approximately 5 minutes with loss of consciousness. These episodes started at the age of two and half years, following chicken-pox infection. The patient was also unable to walk due to weakness of left upper and lower limbs (left sided hemiparesis). The patient is a known case of seizure disorder and had taken no medication.

Patient's birth history was uneventful. However, patient's developmental history was significant with delayed milestones and mental retardation. Patient had not done any schooling, so far. There is no h/o any serious childhood infections, neuro-infection or any trauma.

Physical and Clinical Examination

Patient was a young male, moderately built and nourished& disoriented to time, place and person with irrelevant talking. His general physical examination and vitals were normal. Central Nervous System examination revealed hypertonia in left upper and lower limbs with exaggerated deep tendon reflexes and bilateral extensor plantar response along with fanning of toes in left lower limb. Examination of other systems was unremarkable.

Radiological Examination

M.R.I. Brain: MRI of Brain revealed diffuse atrophy involving the right cerebral hemisphere mainly in the cortical and sub-cortical regions with ex-vacuo dilatation of right lateral ventricle. Multiple gliotic-encephalomalacic areas were seen in right fronto-parieto-temporal lobes.

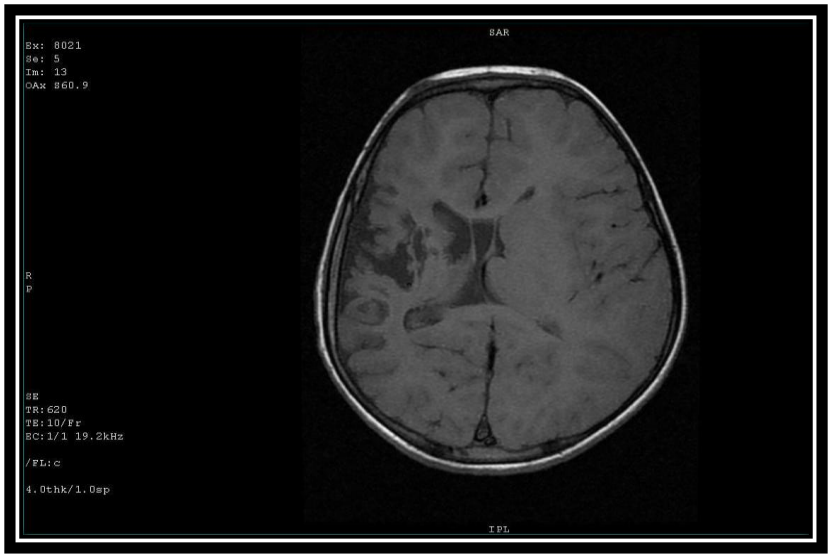

Figure 1: T1-weighted M.R.I. Axial Image showing diffuse right cerebral atrophy

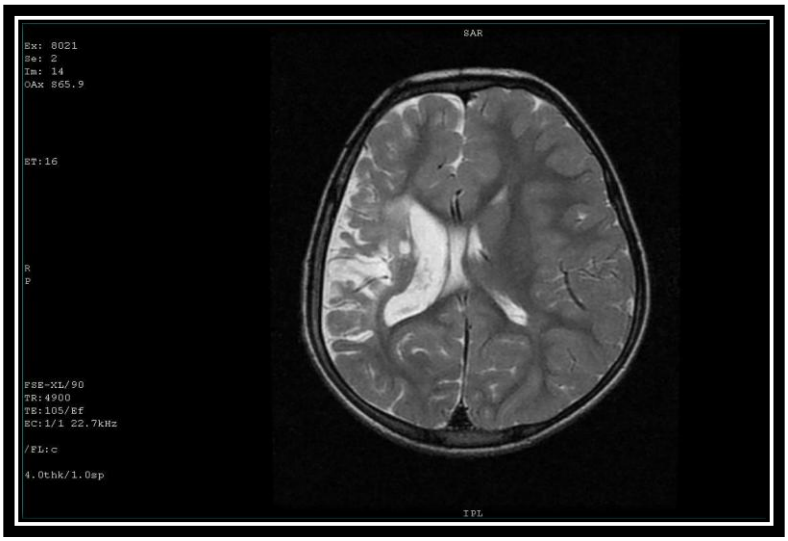

Figure 2: T2-weighted M.R.I. Axial Image showing diffuse right cerebral atrophy withex-vacuo dilatation of right lateral ventricle

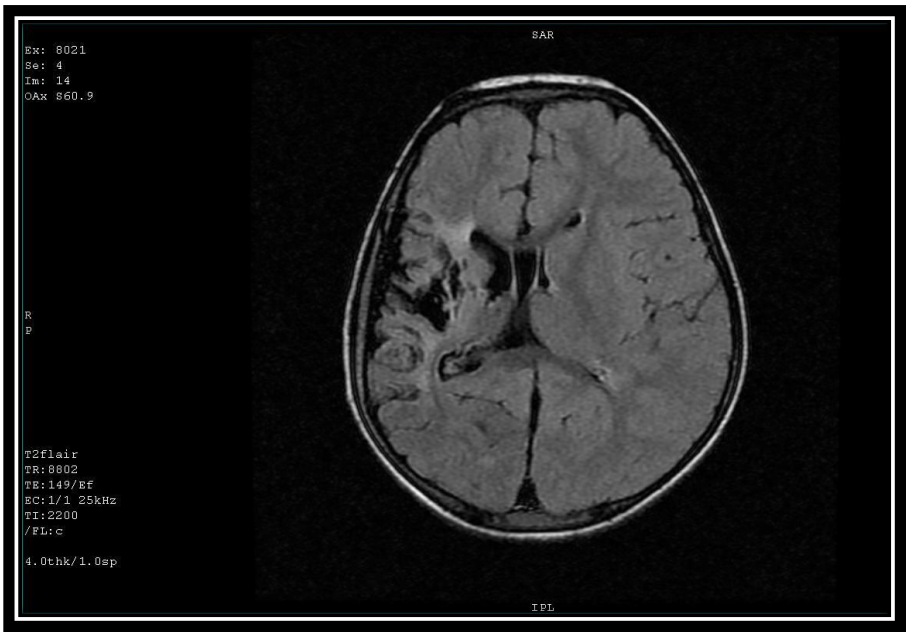

Figure 3: T2 FLAIR-weighted M.R.I. Axial Imageshowing multiple gliotic-encephalomalacic areas in right temporo-fronto-parietal region

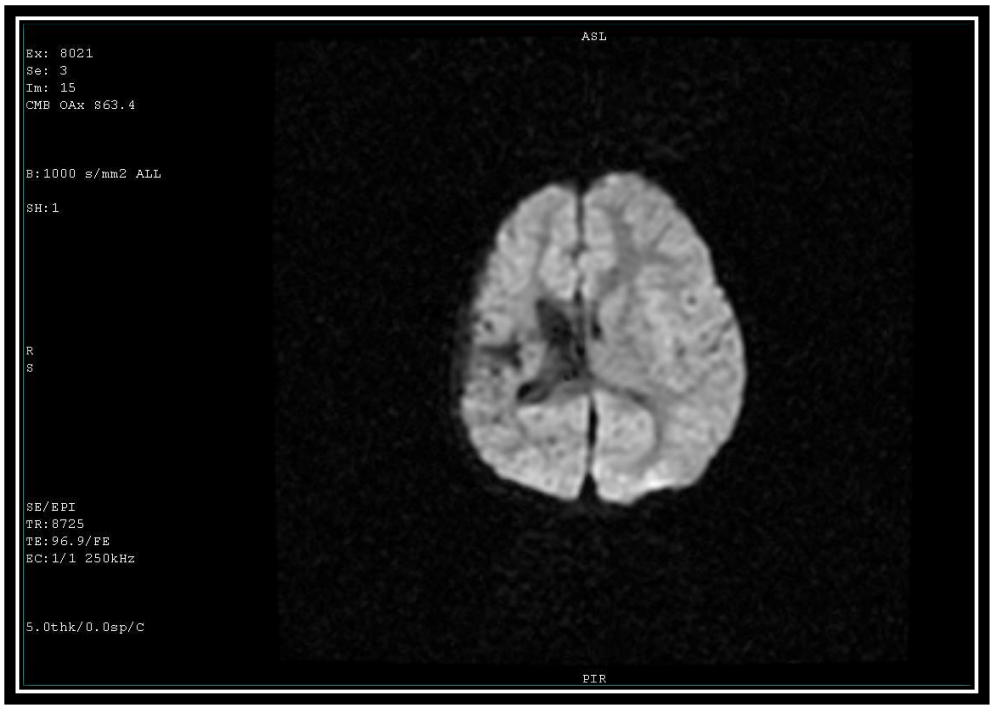

Figure 4: DWI-weighted M.R.I. Axial Image showing diffusion restriction in right parieto-temporal region

The encephalomalacic area appeared isointense to CSF on all imaging sequences while the gliotic area appeared hyperintense on FLAIR images. Persistent cavum septum pellucidum and cavumvergae were seen.

No evidence of any calvarial thickening is seen. Left cerebral hemisphere appeared normal. Brain stem and cerebellar hemispheres also appeared normal.

DISCUSSION

RE is a sporadic chronic inflammatory disease of central nervous system occurring mostly in the pediatric population, first reported by Theodore (1958). The patient presented with intractable focal onset seizures caused by progressive encephalitis. Since the disease is insidious in onset, it is difficult to make early diagnosis. The mean age of presentation is between 6 to 8 years. Both the sexes are equally affected. The etiology of RE is still unclear. Various factors and studies show role of viral infection, while others describing it as an auto-immune pathology involving the antibodies against theprotein of glutamate receptor (GluR3) (Bien *et al.*, 2005; Rogers *et al.*, 1994). Glutamate is an excitatory neuro-transmitter; abnormal antibodies in these patients cross the blood-brain barrier previously breached by seizure activity. They bind and activate glutamate receptors, thus stimulating nerve cells. It is believed that this receptor activation may trigger seizures in these patients (Rogers *et al.*, 1994).

Clinically, patient presents with intractable focal onset seizures, namely Epilepsia Partialis Continua (EPC), followed by hemiparesis and cognitive impairment, which gradually progresses with the disease activity.

Diagnosis of RE is based on classical clinical, neuro- imaging and pathological findings. However, brain biopsy, due to its invasive nature, is not done in all cases. Bien *et al.*, (2005) proposed a Three-Stage natural history of RE on the basis of long term observation of 13 patients (Bien *et al.*, 2005).

The First stage is nonspecific, called the Prodromal stage, manifesting with a relatively low seizure frequency and, rarely, mild hemiparesis (median duration: 7.1 months; range: 0 months to 8.1 years).

The Second stage, called the Acute stage is characterized by an augmentation in the frequency of seizures, often as EPC, and an increase in the degree of hemiparesis (median duration: 8 months; range: 4-8 months).

The Final stage is the Residual stage presents with permanent and stable neurological deficits, mostly severe hemiparesis, and a decreased frequency of seizures.

Bien *et al.*, (2005) also proposed a Five Stage MRI model of RE based on a retrospective study of 39 MRI scans of 10 patients.

Table 1: MRI Stages

Stages	Volume	T2/FLAIR Signal
0	Normal (subclinical)	Normal
1	Swelling	Increased
2	Normal	Increased
3	Atrophy	Increased
4	Atrophy	Normal

The earliest abnormal MRI feature (Stage 1) is cortical swelling with hyper-intense T2/FLAIR signal with an average duration of 0.3-12.3 months. During Stage 2 (average duration: 2.1-22.6 months), the features are focal or multifocal T2 and FLAIR hyper-intensities involving the cortex or white matter of the uni-hemisphere, mostly accentuated at the insular and peri- insular region, progressively spreading across the hemisphere. Histopathology, a higher number of T cells and reactive astrocytes corresponding to areas of higher signals can be revealed at this stage. Later on (Stage 3), (average duration: 4.6- 103.8 months) uni-hemispheric atrophy sets in, characterized by widening of cortical sulci and dilatation of the ipsilateral lateral ventricle. Our patient presented at this stage. Most of the tissue loss occurs during the first 12 months after the onset of symptomatic disease in the majority of patients. The final phase (Stage 4) is characterized by disappearance of the increased signal, leaving a markedly atrophied cerebral hemisphere.

In the early course of RE, the CT and MRI imaging studies may be normal. With the progression of the disease, swelling in the cerebral hemisphere is noted followed by pattern of cortical atrophy. The frontal and fronto-temporal lobes are more commonly involved. The unilateral distribution of cortical atrophy is the key imaging feature that needs to be recognized to diagnose RE.

Magnetic Resonance Spectroscopy (MRS) reveals decrease in N-acetyl aspartate (NAA) and increased or normal choline levels, suggestive of neuronal loss, is seen in RE. The presence of lactate with elevated glutamate/glutamine levels is noted following seizure activity (Wellard *et al.,* 2004).

Gadolinium-enhanced imaging has not been found to have any added advantage for establishing the diagnosis even though there are rare reported instances of gadolinium enhancement in RE, associated with an exacerbation of seizure frequency and neurologic deficits (Hart *et al.,* 1994).

Magnetic Resonance Angiography is useful in excluding large to medium vessel vasculitis as the cause of signal changes, including extremely rare unilateral Moya-Moya disease.

The role of CT in diagnosis of RE is inferior to that of MRI even though imaging features are similar. The signal abnormalities appear earlier on MRI (Bien *et al.,* 2002b).

Fluorodeoxyglucose-positron Emission Tomography (FDG-PET) may show epileptogenic foci as area of hypo-metabolic activity and help towards identifying areas not detected by MRI, especially at early stages of disease (Wellard *et al.,* 2004; Rastogi *et al.,* 2008). Hyperactivity on FDG-PET may also be seen during the immediate postictal phase.

Single Photon Emission Computed Tomography (SPECT) may also show parallel findings and results (Rastogi *et al.,* 2008).

The PET and SPECT also reveal diminished cerebral perfusion as noted in DWI (Diffusion-Weighted Imaging).

Differential Diagnosis

Differential Diagnoses for RE includes- Dyke-Davidoff-Masson Syndrome (DDMS), Sturge-Weber Syndrome (SWS), Hemimegalencephaly, Hemiconvulsion Hemiplegia Epilepsy Syndrome (HHS) and Moya-Moya Disease (unihemispheric cerebral vasculitis).

Dyke Davidoff Masson Syndrome (DDMS) is a set of conditions of different etiologies, leading to unilateral cerebral atrophy with homolateral calvarial hypertrophy and hyperpneumatization of sinuses. The etiology may be classified into congenital and acquired groups. In the congenital variety, cerebral damage usually has a vascular origin. In the acquired type, cerebral insults occur during perinatal period or later and causes include trauma, intracranial hemorrhage, infection and ischemia; and in premature infants, sub-ependymal germinal matrix and intra-ventricular hemorrhage. As the insult to brain occurs much earlier in intrauterine or perinatal period compared to RE, there is a compensatory overdevelopment of paranasal sinuses and mastoid air cells, ipsilateral calvarial thickening and elevation of the petrous ridge, sphenoid wing and orbital roof (Kochar *et al.,* 2001).

Sturge-Weber Syndrome (SWS) is a rare neuro-cutaneous syndrome characterized by facial capillary and capillary-venous malformations in trigeminal nerve distribution, lepto-meningeal venous angiomatosis, seizures, dementia and hemiplegia. Characteristic imaging findings of the cerebral atrophy with gyral or curvilinear calcification (typically described as tram track), enhancing angiomas and ipsilateral enlarged choroid plexus readily differentiate it from RE. Secondary compensatory skull changes to atrophy as in DDMS are also described, but considered as a separate entity (Rastogi *et al.,* 2008; Wellard *et al.,* 2004).

Hemimegalencephaly is characterized by a large unihemisphere with ipsilateral ventriculomegaly as a result of partial or complete hamartomatous overgrowth of cerebral hemisphere. The affected hemisphere may show focal or diffuse neuronal migration defects, with areas of polymicrogyria, pachygyria and heterotopia. The frontal horn of the ipsilateral ventricle appears straight and pointed anteriorly and superiorly with an indistinct cortical– white matter junction and variable degrees of T2 hyperintensity of the white matter due to heterotopia and gliosis. Unihemispheric cerebral vasculitis is very rare even though one adult case showing progressive atrophy of a single hemisphere with signal changes and parenchymal gadolinium enhancement has been reported (Bien *et al.,* 2002b).

The above differential diagnoses were easily ruled out in our patients based on MRI findings.

The outcome of RE is disappointing though early initiation of therapy delays the progression of disease. Treatment includes immunosuppressive and immunomodulator regimens in the form of steroids, IV immunoglobulins and plasma exchange. They are useful during the acute stage but may have side effects. Our patient was also started on anti-convulsants and immunomodulatory therapy and responded well on

follow-up of six months. However, functional hemispherectomy has been the most efficient option to eradicate seizures and prevent further deterioration in cognition (Deb *et al.,* 2005; Hart *et al.,* 1998).

Conclusion

Clinically, RE is characterized by intractable focal onset seizures, namely epilepsiapartialis continua (EPC), and deterioration of functions associated with the affected hemisphere (Oguni *et al.*, 1991).

MRI abnormalities of RE range from initial uni-hemispheric swelling with high signal on T2W and FLAIR images to abnormalities spreading across the affected hemisphere, followed by severe atrophy and disappearance of abnormal signal.

In pediatric uni-hemispheric progressive cerebral atrophy, RE should be considered in the differential diagnosis, especially if there is no intracranial calcification or contrast enhancement.

The radiologist plays a key pivotal role as neuro-imaging is an important tool for early diagnosis and excluding differential diagnoses, which can modify the progression of disease with timely intervention and management.

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