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Analysis of Pediatric Rasmussen Encephalitis: Experience from A Tertiary Care Hospital in Bangladesh

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Abstract

Background: *Rasmussens encephalitis (RE) is rare progressive cerebral inflammatory disease predominantly affecting pediatric population. The key clinical features are seizure and hemiparesis. Seizure is mostly focal with or without epileptia partialis continua (EPC). Diagnosis is established by EEG showing epileptic discharges with focal slowing, focal cortical atrophy in neuroimaging and T cell dominated encephalitis in biopsy or autopsy. This study was done to describe the clinical, laboratory features and treatment of RE in Bangladesh perspective.*

Materials & Methods: *This study was done in Department of Pediatric Neurology, IPNA, BSMMU, Dhaka, Bangladesh. Four admitted children who were diagnosed as RE from January 2016 to July 2019 were included in this study. Retrospective detail data of the all four patients were collected and analyzed.*

Results: *The age ranging was 3-12 years, all were male. Cognitive decline, speech disorder, hemiparesis were observed in all the patients. Among them 1 had prodrome of fever. All the patients had seizure, mostly focal onset. Among them 2 had EPC. Treatment was given mainly with immune modulatory drugs (Intravenous methyl prednisolone, IV immunoglobulin, oral steroids) and antiepileptic drugs. On follow up all the patients had consequences in the form of hemiparesis, epilepsy, dysphasia, cognitive disorder etc.*

Conclusion: *Cognitive decline, speech disorder, focal seizure and hemiparesis were the common presentation. EPC was observed in 50% of cases and consequences on follow up in all cases.*

Keyword: *Pediatric, Rasmussen encephalitis (RE), Epilepsy.*

Introduction:

Rasmussens encephalitis (RE) is a progressive inflammatory disease of brain. It is a devastating disease affecting unilateral cerebral hemisphere causing medically refractory focal seizure, cognitive decline and hemiparesis. It affects predominantly pediatric population, previously healthy children are affected.[1,2] It was first described in 1958 by Theodore Rasmussen.[3] Although some patients may present in adulthood, most of the patients present in childhood. The age at onset is in childhood, between 6 and 8 years (range: 1-13 years). Children may have a previous history of infectious or inflammatory disease during the last 6 months before the onset of the seizure.[4,5] There are three phases usually. First there is a prodromal phase which consists of low seizure frequency and mild of no hemiparesis. Second, there is an acute phase with epilepsia partialis continua and deteriorating limb weakness. Third there is a residual burnt-out phase which consist of stable state with fixed hemiparesis and reduced seizure frequency.[6] The pathophysiology of this disease remains unknown, current hypothesis indicated immune mediated mechanism. This is supported by the pathological specimen of brain and response to immunomodulatory therapy.[7]

There is no study from Bangladesh on RE as it is a rare entity, thus there is a deficit in study of this

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potentially severe disorder. Moreover , till date there is no definite consensus on treatment.[7] However, progress has been made in recent years in understanding clinical evolution, pathogenesis, diagnosis and treatment of RE.[8,9] This study was done to highlights the diagnosis and treatment of RE in a tertiary care centre in Bangladesh.

Materials & Methods

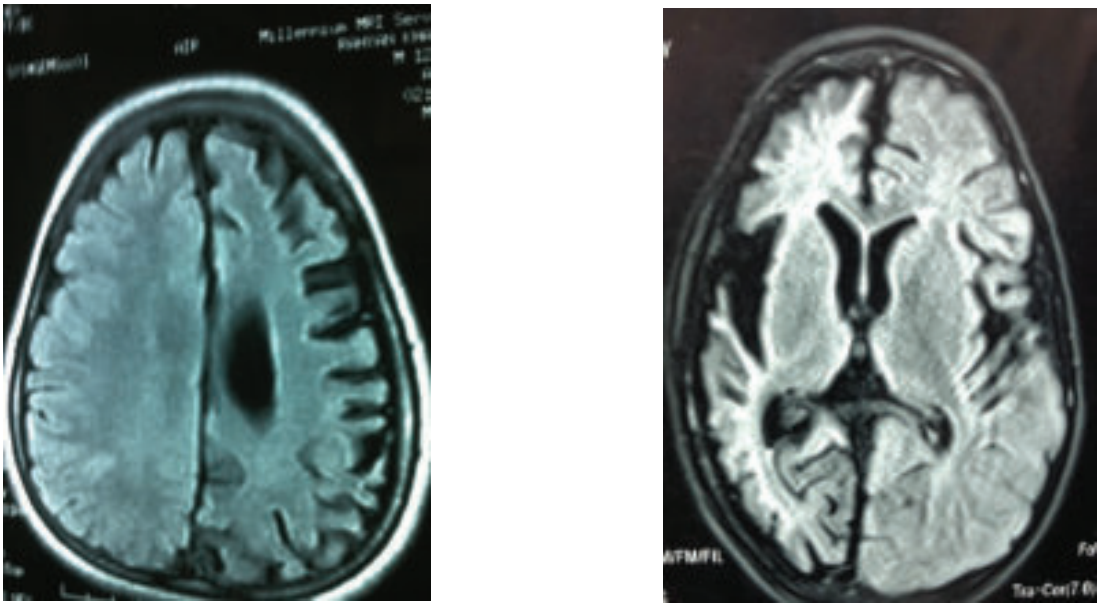
This study was done in Department of Pediatric Neurology, Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Four admitted children who were diagnosed as RE from January 2016 to July 2019 were included in this study. We gathered the clinical data of all four patients retrospectively who were admitted for treatment in that tertiary care center. We took history regarding the demographic profile, antecedent illness, age of onset of seizure, age at presentation, types of seizure, presence of epilepsia partialis continua (EPC), presence of generalized convulsive status epilepticus, age of onset of hemiparesis etc. EPC was defined as regular or irregular clonic twitches affecting a limited part of the body lasting >1 h and recurring at intervals of <10 s. [10] We noted the follow up in the outdoor of the center periodically regarding the change of pattern of seizure, progression of hemiparesis, cognitive status etc. In every patient MRI of brain with contrast and MRA was done. Expert opinion from neuro-radiologist was taken. Follow up MRI was done after 6 months of first MRI. Electroencephalography (EEG) was done in all patients at reception. Then follow up EEG was done at 3 month, 6 month and 1 year as a protocol of the center. Exclusion of other possible causes were done by vasculitis panel (ANA, anti DS DNA, anticardiolipin antibody, antiphospholipid antibody, urine R/E), CSF study to exclude viral causes etc. Data regarding treatment after hospitalization by immunotherapy and antiepileptic drugs were collected & analyzed.

***Case 1*:** A 12 year male, was previously normal, 2nd issue of nonconsanguineous parents, presented to us with history of seizure for 7 months. Before the onset of seizure, there was a prodrome of upper respiratory tract infection. Seizure was focal in nature, started from left upper limb, then occurred in left lower limb, clonic in nature. There was associated facial twitching. Seizure was increasing in frequency progressively. Initially he did not have any focal deficit, but after one month of onset of seizure he developed left sided hemiparesis. He was going to school with average school performance. Gradually, his school performance deteriorated and ultimately he failed to attend school. Meanwhile he developed two episodes of status epilepticus, focal with secondary generalized in nature, needed hospital admission.

His first MRI at the time of onset showed nonspecific finding. Second MRI after 6 months showed atrophy of left hemisphere, atrophy of head of caudate nucleus along with T2 hyperintensity of frontal and parietal areas of left hemisphere ***(Figure 1A).*** First EEG at the time of diagnosis showed focal discharge from left temporal and frontal regions, background showed disturbed. The follow up 2 EEG showed features of epileptic encephalopathy (multifocal discharge, generalized background slowing). His seizure was not controlled but decreased in frequency, with several antiepileptic drugs. At 2 year follow up, he had hemiparesis (improved), epilepsy, speech difficulty and cognitive decline.

Case 2: A 3 year boy, with normal development presented with seizure. Prior to seizure, he has a history of fever for 5 days, high grade continuous in nature. Two weeks after the onset of fever, seizure started. Seizure was focal tonic-clonic in nature, increased in the next 7 days. Then he developed epileptia partials continuea (EPC). He was hospitalized, treated with Injectable anticonvulasants (Phosphenytoin, phenobarbitone) but seizure was not subsided completely. He was discharged with oral antiepileptics. He was followed for next 3 years. He developed hemiparesis and cognitive decline and speech difficulty (dysphasia) in the mean time. His initial

MRI was normal. As seizure was increasing, a repeat MRI was done after 1 year. It showed atrophy of right hemisphere with hyperintensity of frontal and parietal areas. ***(Figure 1B)*** First EEG at onset of seizure showed focal epileptic discharges from frontal and parietal regions of right side. Background was normal. The second EEG after 1 year showed near continuous epileptic discharges, multifocal, mostly arising from right frontal, parietal and temporal regions, background was disturbed. Patient was treated initially with antiepileptic drugs (Sodium Valproate, oxcarbazepine, clobazam). After diagnosis of RE immunotherapy was started with IV methylprednisolone followed by oral prednisolone.



A B

Figure 1: *A: MRI of brain of Case 1 showing hemiatrophy of left cerebral hemisphere. B: MRI of brain of case 2 showing hemiatrophy of right hemisphere with hyperintensity of cortex.*

Case 3: A 12 year boy presented to the emergency department with the complaints of seizure and loss of consciousness. He had no prior history of prodrome or fever. He was 2nd issue of nonconsanguineous parents, had prior normal development with no neurodevelopmental deficit. After admission, the child developed status epilepticus and was shifted to ICU. He was managed with anticonvulsants for SE as per protocol. It turned into super-refractory SE and continuous seizure persisted for about 7 days. Meanwhile all routine blood test was done which was nonspecific, CSF study was normal, EEG showed diffuse slowing. MRI of brain showed cerebral edema in left hemisphere. On the basis of this reports he was treated with immunotherapy (IV immunoglobulin and IVMP) followed by oral steroid (12 weeks). After 7 days the child gained consciousness, then he gradually was improving. At 2 week he was discharged with oral anticonvulsants (sodium valproate, clobazam, levetiracetum). At the time of discharge, he was having infrequent seizure with no focal deficit. We followed him for 4 years. In the mean time he developed progressive hemiparesis on right side of body, right sided facial palsy (upper motor type), speech difficulty and cognitive decline. He never developed SE but he continued to developed seizure even on multiple drugs. His repeat EEG showed multifocal epilepsy with background abnormality and MRI showed atrophy of left hemisphere with atrophy of head of caudate nucleus with hyperintensity of frontal, parietal and occipital regions.

Case 4: A 4 year old boy presented to outdoor with the complaints of seizure for 2 months. Seizure was clonic in nature, occurring in right upper and lower limbs with facial twitching. He also had difficulty in speech for 1 month. Gradually he progressed to continuous partial seizures in right upper limb and right sided hemiparesis. Mother also complained that he had cognitive decline manifested by could not identify his family members and he also developed apathy. He had a normal development prior to onset of seizure and normal perinatal period. None of his family member had similar type of illness. He did not have any prodrome of fever or respiratory tract infection. His routine blood test, CSF study was normal. EEG showed epilepsia partialis continua .MRI of brain showed hemiatrophy of left hemisphere, T2 hyperintensity of left frontal area (periventricular), MRA was normal. Considering the above factors he was diagnosed as RE. He was treated with immunotherapy (IVMP) for 5 days (30mg/kg/day) followed by oral prednisolone for about 8 weeks. The following antiepileptic drugs were given: I/V phenobarbitone, I/V fosphenytoin, levetiracetum, Na Valproate, oxcarbazepine, clobazam etc.

At 1 year follow up, he had intractable seizure (1-2 episodes /day), hemiparesis, behavioural abnormality (hyperactivity), aphasia.

Table-I

Demographic characteristics and clinical features of the studied subjects

	Case 1	Case 2	Case 3	Case 4
Age of onset	11.5	3	12	4
Age of diagnosis	12	4	12	5
Sex	Male	Male	Male	Male
Prodromal symptoms				
Fever	No	Yes	No	No
Cough/runny nose	Yes	No	No	No
Diarrhoea	No	No	No	No
Vomiting	No	No	No	No
Seizure	Focal, clonic	Focal, tonic-clonic	Focal, tonic, clonic	Focal clonic
Status epilepticus	Yes	No	No	No
Epilepsia partialis continua	Yes	Yes	No	No
Hemiparesis	Yes (left)	Yes (left)	Yes (right)	Yes (right)
Cognitive decline/memory loss	Yes	Yes	Yes	Yes
Speech disorder	Yes (dysphasia)	Yes (slowing of speech)	Yes (slurred)	Yes (dyspahasia)
Loss or altered level of consciousness	No	No	Yes	No
Facial palsy	No	No	Yes (upper motor type)	No

Table-II

EEG features of studied subjects

	Case 1	Case 2	Case 3	Case 4
1st EEG				
Background	Diffuse slowing	Normal	Focal slowing	Disturbed
Epileptic discharge	Focal discharge	Focal discharge	No	Focal discharge
Status epilepticus	No	No	No	No
Epilepsia partialis continua	No	Yes	No	Yes
Epileptic encephalopathy	No	No	No	No
2nd EEG				
Background	Diffuse slowing	Focal slowing	Focal slowing	Disturbed
Epileptic discharge	Multifocal	Multifocal	Multifocal	Focal
Status epilepticus	No	No	No	No
Epilepsia partialis continua	No	No	No	No
Epileptic encephalopathy	No	No	No	No
3rd EEG				
Background	Disturbed	Not done	Disturbed	Focal slowing
Epileptic discharge	Multifocal	-	Multifocal	Focal
Status epilepticus	No	-	No	No
Epilepsia partialis continua	No	-	No	Yes
Epileptic encephalopathy	Yes	-	Yes	No

Table-III
Neuroimaging (MRI of brain) of studied subjects

	Case 1	Case 2	Case 3	Case 4
1st MRI				
Normal /nonspecific	Yes	Yes	No	No
Cerebral oedama	No	No	Yes	No
Hemiatrophy	No	No	No	Yes (right)
Cortical hyperintensity	No	No	No	Yes
Frontal				Yes
Parietal				No
Temporal				No
Occipital				No
Ventricular enlargement	No	No	No	Yes
Caudate nucleus atrophy	No	No	No	No
MRA of brain	Not done	Not done	Not done	Normal
2nd MRI				
Normal /nonspecific	No	No	No	No
Cerebral oedama	No	No	No	No
Hemiatrophy	Yes (left)	Yes (right)	Yes (left	Yes (right)
Cortical hyperintensity				
Frontal	Yes	Yes	Yes	No
Parietal	No	Yes	Yes	No
Temporal	Yes	No	No	No
Occipital	No	No	Yes	No
Ventricular enlargement	Yes (left)	Yes (right)	Yes (left)	Yes (right)
Caudate nucleus atrophy	Yes (left)	No	Yes	No
MRA of brain	Normal	Normal	Normal	Normal

Table IV
Treatment profile of studied subject and follow up

	Case 1	Case 2	Case 3	Case 4
Immunotherapy				
IVMP only	Yes	Yes	No	Yes
IVMP and IVIG	No	No	Yes	No
Maintenance therapy: oral steroid	Yes (6weeks)	Yes (8weeks)	Yes (12weeks)	Yes (8weeks)
Antiepileptic drugs	PHB, LEV, SVA, TPM, OXC	I/V PHB, I/V FPHT, SVA, OXC, CLB	I/V FPHT, I/V PHB, LEV, LTG, OXC, TPM, CLB, CLN	I/V FPHT, I/V PNB, LEV, OXC, CLB
Outcome				
Time	2 year	3 year	4 year	1 year
Complete recovery	No	No	No	No
Hemiparesis	Yes	Yes	Yes	Yes
Epilepsy	Yes	Yes	Yes	Yes
Speech disorder	Yes	Yes	Yes	Yes (aphasia)
Cognitive decline	Yes	Yes	Yes	No
Behavioural disorder	No	No	Yes	Yes (hyperactivity)
Ambulatory	Yes	Yes	Yes	Yes
Going to school	Yes	No	No	No

IVMP-Intravenous methylprednisolne, IVIG-Intravenous immunoglobulin, SVA-Sodium Valporate, PHB- Phenobarbitone, FPHT-Fosphenytoin, LEV-Levetiracetum, LTG-Lamotrigine, OXC-Oxcarbazepine, TPM-Topiramate, CLB-Clobazam, CLN-Clonazepam

Discussion:

RE is a rare form of neurologic disorder characterized by progressive cerebral hemiatrophy and medically refractory epilepsy.[7] We are reporting a case series of 4 cases highlighting the core clinical criteria, MRI of brain profile, EEG profile, treatment and outcome. This will help to recognize and treat this rare disorder.

Some clinical features are very characteristic of RE like intractable focal epilepsy, cognitive decline and hemiparesis.[2] All three core criteria are present in all cases of this study. There are three well-documented phases of the disease: a prodromal phase with an intermediate frequency of focal seizures and no static neurologic deficits, an acute phase marked by more frequent seizures, hemispheric volume loss, and deficits attributable to that atrophy, and lastly a residual phase with fewer seizures, marked hemiatrophy and severe neurologic deficits.[6] Except case 3, all the cases of this study followed this paradigm. Although the time span of the stages were different in different cases. In case three, the patient initially presented with severe seizure although then he did not show any focal deficit.[5,11] (Table-I) also divided the course of the disease into 3 stages on the basis of a review of 48 patients with RE. In this model, stage 1 correlates to the development of seizures until the hemiparesis is established (3 months – 10 years, mean: 3 years). During this stage, the seizures frequency and intensity progressively increase. Stage 2 is characterised by a fixed hemiparesis and additional neurological deficits including intellectual decline (2 months – 10 years, mean: 3.7 years). Moreover, there is an increase in seizure frequency and intensity; seizures may even be continuously present. Stage 3 is marked by the stabilization of the disease and a decrease of seizure activity. The neurological deficit is established, such as spastic hemiparesis, visual field and sensory deficits. There may be additional intellectual disability which can range from mild to severe grades.[5,11]

RE usually affects previously healthy children and adolescents between the ages of 14 months and 14 years.[12] However, adults may rarely be affected.[13] The age of onset in our cases was 3-12 years. All four cases are male in our study. However, in has been mentioned in literature that in RE there is no sex, geographical, and ethnic predominance. [14] Although a case series reported by Prabal D reported male predominance.[15] Epilepsy is mentioned as partial or generalized tonic clonic seizure which may progress to EPC. The seizure is mostly drug -resistant. All the patients in this study had focal seizure, 2 had EPC and seizure was pharmaco-resistant. In literature speech disturbance has been mentioned which was present all 4 cases of our study. Although bilateral involvement has been mentioned, but all our cases had unilateral involvement.[2,12,16,17]

The aetiology and pathogenesis of Rasmussen's encephalitis still remain unknown. There are three hypotheses: (a) a direct viral insult, (b) an autoimmune process triggered through a viral agent, (c) a primary autoimmune process.[4,5,18]

Both EEG and MRI of brain play important role in diagnosis of RE. Bien et al have proposed a 5 stage model based on magnetic resonance imaging (MRI).[6] Stage 1 shows no abnormality, stage 2 shows oedema and increased signals, stage 3 reveals increased signals with normal hemispheric volume, stage 4 shows increased signals with hemispheric atrophy, and in stage 5 there is a disappearance of the increased signal, leaving a markedly atrophied cerebral hemisphere (cortical and subcortical). In this regard in 1st MRI, our case 1 and case 2 were in stage 1, case 3 in stage 2 and case 4 in stage 4. However, in 2nd MRI case 1, 2, 3 were in stage 4 and case 4 was in stage 5. Ipsilateral atrophy of the head of the caudate nucleus is a typical but not an invariable feature of RE. Only one case had this feature in our case series. It is here to mention that, serial MRI is important for identifying the pattern of RE which was also observed in our case series.[6] Bihemispheric involvement is rare and is associated with fatal outcome. [19] (Table III)

RE does not have any specific type of EEG which can differentiate it from other types of focal epilepsy. But change in repeat EEG with the advent of disease is very important here. Usually initially there is normal EEG, then there is persistent high amplitude delta activity. Widely varying abnormalities in electro-encephalograms (EEG) are seen in patients with Rasmussen's encephalitis, which are often related to clinical progression. No specific EEG abnormalities can distinguish Rasmussen's encephalitis from other causes of focal epilepsy. However, from an initially normal EEG, persistent high amplitude delta activity develops along with epileptiform discharges. There may be features of SE or EPC. [2,20] In our case series, the progressive deterioration of the background, intermittent focal epileptic discharge were observed.

On initial EEG, only one case showed no abnormality, but all other cases showed abnormality particularly in background. (Table 2)

Currently there is no consensus in treatment of RE. The mainstay of treatment is immunomodulatory therapy, antiepileptic drugs and epilepsy surgery.[7] All the 4 cases in this case series have been treated with high dose intravenous methyl prednisolone. Only the case 3 was treated with intravenous immunoglobulin. We continued oral steroid for a duration of 6-12 weeks in our cases. (Table 4) In related studies it has been seen that immunomodulatory therapy were given with high-dose steroids, intravenous immunoglobulin (IVIG) , plasma exchange , azathioprine , tacrolimus , natalizumab and rituximab.[21-32] We did not use plasma exchange or any other immunomodulatory drugs except steroid and IVIG. Immunotherapy has been proved to be slow the progression of the disease. In some studies, it has been mentioned as curative. However, early immunotherapy has been recommended.[14,32,33] Moreover, long term immunotherapy has also been suggested with either steroid or other immunomodulatory drugs like tacrolimus.[34,35]

Antiepileptic drugs (AED) are another modality of treatment in RE. It is here to mention here that these drugs do not halt the progression of disease but limit the morbidity.[36] One of the predominant type of seizure is EPC which tends to drug resistant.[14] In this case series, we used both oral and injectable AEDs for optimum seizure control. Seizure freedom could not be achieved in any of the case however, decrease in the frequency of seizure was achieved. We used phenobarbitone, fosphenytoin, oxcarbazepine, Na valproate, levetiracetum, topiramate, benzodiazepines, lamotrigine etc. In some related studies, botulinum toxin was used for EPC. Other modalities applied were vagus nerve stimulation and transcranial magnetic stimulation.[37,38,39] None of these treatment was administered in our study due to financial and logistic issues.

Till date timely and appropriate surgery is the curative treatment of RE but it has functional complications. The modalities of surgery are hemidisconnection, hemispherectomy, hemispherotomy etc. Early surgery can prevent cognitive impairment associated with poorly controlled epilepsy.[14, 40, 41] None of the cases in our study had undergone surgery.

The outcome of RE is disappointing in the most of the cases. Early treatment and surgery can halt the progression of disease.[42] We followed up the patients for a period of 1-4 years, none of the patients were seizure free, all had hemiparesis, speech disorders. We also observed cognitive decline in 3 of the patients, behavioural problems in 2 of the patients. Only one patient was school going however all the patients were ambulatory during our follow up. Our case series had similarity with the reported cases where the drug resistant focal seizure, hemiparesis, hemianopia, cognitive decline, dysphasia were the consequences in follow up period. [32,34] (Table- IV)

Conclusion:

We presented a case series of RE with definite clinical features, EEG and neuroimaging finding, treatment along with short term outcome from a developing country perspective. Cognitive decline, speech disorder, focal seizure and hemiparesis were the common presentation. Epilepsia partialis continua (EPC) was observed in 50% of cases and consequences on follow up in all cases.

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