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Waleed Shahzad
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Muhammad Hassan
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Haris Majid Rajput
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Tehmina Inayat
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Naveed Ullah Khan
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

See next page for additional authors

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Authors

Waleed Shahzad, Muhammad Hassan, Haris Majid Rajput, Tehmina Inayat, Naveed Ullah Khan, and Mazhar Badshah

A RARE CASE OF EPILEPSIA PARTIALIS CONTINUA SECONDARY TO RASMUSSEN'S ENCEPHALITIS

Waleed Shahzad[1], Muhammad Hassan[2], Haris Majid Rajput[3], Tehmina Inayat[4], Naveed Ullah Khan[5], Mazhar Badshah[6]
[1,2,3,5,6] Department of Neurology, Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan
[4]Department of Internal Medicine, Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Correspondence Author: Waleed Shahzad, *Department of Neurology, Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan* ***Email:*** *valeed@live.com*

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ABSTRACT:
Rasmussen's encephalitis is a rare baffling disorder seen in nearly 1 % to 2 % of epilepsy population and in 7.4% of paediatric population. It is mostly seen in children and in most cases seizures are seen during 14 months to 14 years with peak age 3 to 6 years. Etiology includes viral infections, humoral autoimmunity and T-cell mediated cyto-toxicity of the brain tissue. The main clinical features are intractable epilepsy, hemiparesis, hemidystonia, hemiathetosis, epilepsia-partialis-continua and mental decline. Imaging shows unilateral hemispheric brain atrophy. Here we describe a unique case of a 15-year-old Pakistani girl with severe immune mediated brain disorder characterized by unilateral hemispheric atrophy,progressive neurological dysfunction and intractable seizures. Literature on Rasmussen's encephalitis following is sporadic with very few publications. This clinical entity should be kept in mind when a patient presents with intractable refractory seizures. Early recognition and treatment is beneficial to prevent adverse outcomes.
KEY WORDS: Rasmussen's encephalitis, epilepsia-partialis-continua, humoral auto immunity, T-cell mediated cyto-toxicity

INTRODUCTION:

In 1958 the term 'Rasmussen Encephalitis' was first penned down by Theodore Rasmussen and co-workers.[1] It is a baffling inflammatory disease of the brain with un-known origin which results in one sided brain atrophy, intractable-focal-seizurescalled epilepsia-partialis-continua (EPC), progressive weakness of limbs (hemiplegia)and progressive cognitive decline.[2] EPC is a term used for continuous focaljerking of the body involvingdistal limbs and doesnot halt like the usual time for focal seizures. EPC is now considered as a form of focal-status-epilepticus.[3] Rasmussen's is seen primarily in children under age of 10 years and in most cases seizures occur from 14 months to 14 years with peak age 3 to 6 years.[4] Adults are not commonly affected and only 10% of the total cases account for adult populating being affected.[4] Patho-physiology is still unclear but many theories have been proposed which include viral infections, humoral auto immunity and T-cell mediated cyto-toxicity of the brain tissue against viral proteins present in the neurons.[5] Rogers et al. found involvement of antibodies against glutamate-receptor-(GluR3) and viral agents like cytomegalo virus and herpes-simplex-virus in the etiology of Rasmussen's.[6] However, anti-GluR3 are not specific since they do not differentiate Rasmussen's from other epilepsies of non-inflammatory origin.[6]

Bien diagnostic criteria for Rasmussen's is clinically applied which consists of clinicoradiological features including focal seizures with EPC and unilateral cortical deficits together with uni-hemispheric focal cortical atrophy on brain imaging. Electroencephalogram (EEG) findings are suggestive of uni-hemispheric slowing with epileptiform activity. However, if EEG is not supportive than histo-pathology findings are considered which show T-cell mediated encephalitis with activated microglial cells and reactive gliosis.[7] There are different treatment options applicable which are selected according to patient's needs including anti-epileptics, immune-therapy and surgical options. Seizures in Rasmussen's are highly resistant to any kind of medical therapy. Despite poor to no response of focal fits to anti-epileptic drugs, they are still needed for generalized tonic clonic seizures as in our case. Cortico-steroids, Intravenous immunoglobulins, plasma-exchange, Tacrolimus (T-cell inhibiting immunosuppressant), Cyclo-phosphamide, Mycophenolate-mofetil and Rituximab all have shown effective results for short term treatment but have not shown promising results for long term treatment.[8] Surgical treatment i.e. hemi-spherectomy has proven to arrest the disease cascades in most patients but has serious post-operative neurological deficits like spastic

hemiplegia, homonymous hemianopia and language problems.[9]

CASE PRESENTATION

A 15-year-old Pakistani female presented in the emergency room with history of left sided focal-seizures involving left half of the face and body with secondary generalization, impairment of consciousness, frothing from mouth, tongue bite and lateral rotation of neck. Upon arrival she was given diazepam, levetiracetam, thiamine, calcium and dextrose infusion and at the same time computed tomography of the brain and blood tests were performed. After acute treatment she was shifted to neurology ward and started on phenytoin and lacosamide. Her generalized seizures subsided while she had continuous jerking of left side of the face and body.Her past history revealed that she had developed these symptoms since the age of 5 years after a spike of fever. She was started on carbamazepine at that time but her seizures remained intractable to the point that some years later she developed left hemiparesis with hemiplegic gait and left hemidystonia. Her family history, birth history and developmental history were normal. Her vaccination status was complete. On general physical examination her vital signs were normal. She had left hemiplegic gait, left hemi dystonia and continuous fits involving left side of the face and body. Mini mental state examination showed mild to moderate cognitive decline.Glasgow Coma Scale showed score of 15/15. Cranial nerves were intact.Her muscle bulk and tone was normal in limbs. She had a power of 3/5 on the left side with intact reflexes and sensations. Her plantars are bilaterally flexors. Coordination and cerebellar signs were normal. Signs of meningeal irritation were not present. Her respiratory, cardiovascular and gastro-intestinal systems showed no abnormality.Upon investigations her complete blood picture, blood cultures, ESR, detailed metabolic profile, electrolytes, arterial blood gases, lipid profiles, blood sugars, thyroid functions, B12/folate, toxicology screening and auto-immune profile all showed normal results. Her CSF showed normal cytology, normal proteins including screening for herpes-simplex in CSF which came negative. Electrocardiogram and echocardiography showed normal rhythms and ejection fraction with no valvular abnormalities. CT and MRI brain (Figure A) showed hemiatrophy of right cerebral hemisphere. EEG showed background activity consisting of symmetrical posterior dominant low to medium amplitude alpha rhythm. Spike and wave epileptiform discharges were noted in 'right' sided leads (Figure B). She was diagnosed as a case of 'Epilepsa Partialis Continua secondary to Rasmussen's Encephalitis'. Despite being on multiple anti-epileptic drugs with no significant response we started our patient on pulse methylprednisolone therapy (400mg/m2 body surface) for 5 days which was followed by plasma-exchange (five sessions on alternate days). Later she was started on oral tacrolimus therapy (2 tablets x BD) at a liver transplant dose of 0.27 to 0.80mg/kg/day. Patient is currently under our follow up regarding regression of symptoms, anti-epileptic drug level monitoring and keeping track of the side effects of tacrolimus therapy. So, far no serious adverse effects have been encountered by our patient. Her epilepsa partialis continua has improved with no further deterioration of the hemiatrophy and disease process on the follow up MRI Brain.

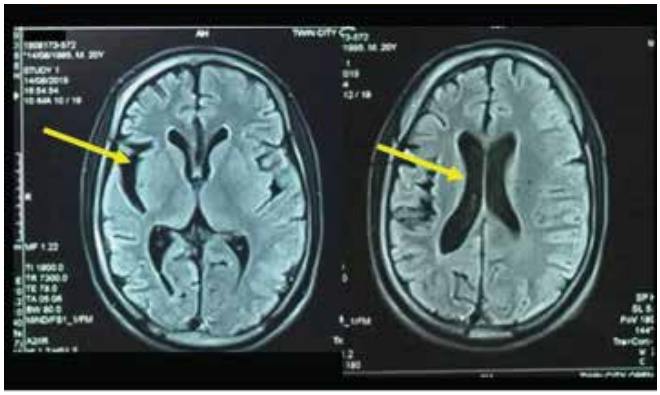

Figure A:MRI brain FLAIR axial showing prominent cortical sulci, gyri and sylvian fissure overlying convexity of right cerebral hemispheres with evidence of volume lossandprominent right ipsilateral lateral ventricle.

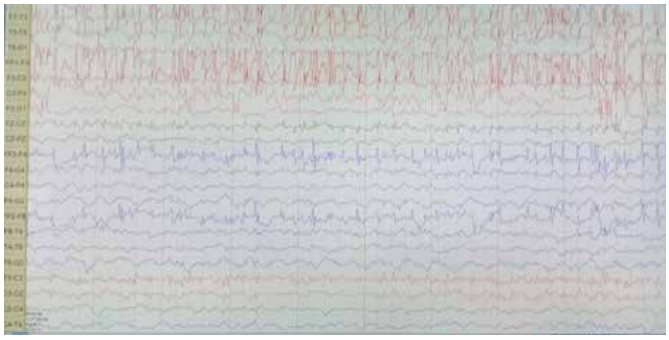

Figure B:EEG showing Spike and wave epileptiform discharges.

DISCUSSION:

Treating this rare clinical entity is a challenge for

clinicians. The main stay of treatment in Rasmussen's is focused to inhibit refractory seizures and to halt progression with the use of immune-modulatory drugs and surgical treatment.Seizures in such patients are refractory to majority of antiepileptic drugs . Many combinations have been experimented but none have proven to be standard. Our patient had a typical clinical and radiological presentation with intractable seizures, left hemiplegic gait and left hemi dystonia. She was inititally managed on conventional anti-epileptic drugs like diazepam, levetiracetam, phenytoin, lacosamide, lamotrigine and clonazepam.These anti-epileptic drugs were used from the time of her presentation to emergency till admission in neurology ward but all these regimen showed no significant response. However,our patient showed considerable improvement of her seizures and cognitive function once she was treated with immune-modulatory agents.

Intravenous-immunoglobulins were not opted due to financial constraints but pulse steroids followed by plasma-exchange sessions and tacrolimus proved to be an icing to the cake.

Our patient qualifies for surgical hemi-spherectomy but it was not opted due to limited resources of the family, post operative complications and unavailability of qualified experienced neuro-surgeons for the procedure. However, a recent study on functional hemi spherectomy in Rasmussen's encephalitis has shown considerable prognosis and positive results with seizure free intervals without aggravation of hemiplegia and a better cognitive outcome following a 2 year period.[10] Recently, many long-term treatments have been tried which include corticosteroid treatment with Intravenous Immunoglobulin (IVIG), treatment with plasma-exchange and oral Tacrolimus therapy.[11] Only few patients have been treated with Rituximab as an alternative therapy in RE.[11]

CG Bien (et al) had studied effects of Tacrolimus therapy in Rasmussen's encephalitis; out of 7 tacrolimus-treated RE patients, the unihemispheric destructive process was significantly slower than in the 12 historical untreated control patients as judged from the progression rate of hemiatrophy. The treated patients had a significantly lower increase in hemiparesis. Only one of six tacrolimus-treated patients showed a cognitive decline.[11]

Compared with the unequivocal observation of a progressive decline in RE, this is a surprisingly positive result. Finally, none of the tacrolimus patients, but 7 of 12 control subjects, proceeded to hemispherectomy. No relevant tacrolimus side effects have been observed over a total of 12.7 patient–years. Disease duration at initial assessment, time of follow-up, and initial seizure frequencies in the control group were not different from those of the treatment group. However, it cannot be excluded that the control patients had more severe disease, as may be indicated by their initial higher hemiparesis grades.[5] The study results suggested a discrepancy between the positive effect of tacrolimus on conservation of motor and cognitive function and brain tissue at one end and the absence of an effect on seizure frequency, on the other.[11] It is open if the advantages of the motor and neuropsychological performance will last or if these patients will further deteriorate and eventually come to hemispherectomy.

Our patient was given surgical option and was referred to an experienced surgeon in another hospital but patient's family refused to opt for the procedure. She is currently on conservative anti-epileptic drugs and oral tacrolimus therapy (2 tablets x BD at a liver transplant dose of (0.27 to 0.80mg/kg/day). Her epilepsia partialis continua has been been considerably well controlled for the last 1.5 years. Her follow up brain MRI did not reveal any further deterioration of hemiatrophy and she had no further cognitive decline. However, generalized seizure frequency was variable with anti-epileptic drugs and oral tacrolimus therapy.

CONCLUSIONS

The initial course of Rasmussen's Encephalitisis frequently distinguished by non-specific features and it may be months or even years before the diagnosis becomes evident. Neuro-imaging is important in all epilepsy syndromes. A patient who is taking two or more than two anti epileptics drugs and still having intractable seizures, neuroimaging must be done to rule out other alternative pathologies and underlying immune mechanisms. Oral tacrolimus therapy and functional hemi-spherectomy has proven to arrest the disease cascades in most patients therefore both the treatment options should be explained to the family sooner or later considering all the pros and cons.Early recognition and treatment is beneficial to prevent adverse outcomes.

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Waleed Shahzad; data collection, data analysis, manuscript writing, manuscript review
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Haris Majid Rajput; concept, data analysis, manuscript review
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Naveedullah Khan; data analysis, manuscript review
Mazhar Badshah; concept, data analysis, manuscript review