Limited chronic focal encephalitis: Another variant of Rasmussen syndrome?
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Limited chronic focal encephalitis

Another variant of Rasmussen syndrome?

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ABSTRACT

Objective: To describe a more limited and less malignant form of Rasmussen encephalitis (RE).

Methods: Three subjects (all women; 37, 31, and 32 years of age) developed childhood or late onset chronic focal encephalitis, with a relatively nonprogressive form of the disorder.

Results: In our patients, clinical features were dominated by partial seizures without marked focal motor deficit and in two with choreo-dystonic movements. The diagnosis of RE was supported by histologic examination and anatomic and functional MRI.

Conclusions: These cases extend the phenotypic presentations of Rasmussen encephalitis and confirm Theodore Rasmussen’s suggestion that there may be mild and nonprogressive forms of the disease. Neurology® 2008;70:374–377

GLOSSARY

RE – Rasmussen encephalitis; VGKC – voltage-gated potassium-channel.

Chronic encephalitis and epilepsy (Rasmussen syndrome) usually manifests with extensive hemispheric involvement and obvious progressive loss of tissue associated with intractable focal epilepsy, epilepsy partialis continua, and other forms of status epilepticus and with progressive focal neurologic deficit. The late Theodore Rasmussen postulated early the presence of a limited and relatively non-progressive form of the disorder. Evidence for such more limited involvement, both in childhood and adult forms, has previously not been reported or emphasized.

Here we present three patients, two with a long history of partial seizures without significant progression or the development of marked focal neurologic deficit. In one patient, the epilepsy was followed by the appearance of involuntary movements and one patient presented in adult life with choreoathetosis followed by focal seizures both remaining localized as well.

CASE REPORTS Patient 1. At the age of 31, this woman developed choreoathetotic movements of the left upper limb with a dystonic posture of the neck and trunk. She was examined 2 years later. Past and family histories were unremarkable. There were no abnormalities on neurologic examination beyond the choreoathetotic movements. She had no awake, sleep deprived, or polygraphic EEG abnormalities and her MRI was normal. There were no acanthocytes.

Three years after the onset of the abnormal movements, a repeat MRI showed mild atrophy of the right caudate nucleus. Six months later, she was admitted to hospital because of worsening of her left sided choreoathetotic movements and the appearance of sporadic focal seizures characterized by strange feelings in her mouth described as a bitter taste, associated with fear and sometimes with auditory hallucinations. Attacks lasted seconds and recurred weekly. Awake and asleep EEG showed slow sharp wave activity over the right temporal region activated by non-REM sleep. Her second MRI revealed an increased signal without swelling of the right temporal insular structures and of the right caudate nucleus. There was also a moderate atrophy of the head of the right caudate nucleus and the corpus striatum with a mild dilatation of the horn of the right lateral ventricle (figure 1, A and B). After 5 months, a third MRI showed a similar increased signal of the right temporal insular structures. In comparison with the previous MRI, a marked dilatation of the sylvian fissure and temporal horn was evident (figure 1, C and D). In comparison with the previous MRI, there was a much increased atrophy of the head of the right...
Patient 1. A 31-year-old right-handed woman had no antecedent or family history of epilepsy. She reached normal developmental milestones and completed a university degree in geography. There was no history of head injury, CNS infection, or febrile convulsions.

Her seizures began at the age of 24 years. She had very frequent episodes of aura with a rising sensation in her epigastrum, severe fearfulness, often followed by partial complex or generalized seizures, postictal headache, and sleepiness. Attacks tended to occur in clusters every 2 to 3 months. At times she would have runs of complex partial seizures for the whole day in what amounted to complex partial status epilepticus. Her seizures changed over a period of years to complex partial seizures of extratemporal type, occurring particularly at night and taking the form of short seizures with complex motor behaviors involving the lower limbs, and without the sense of fearfulness. Neurologic examination showed no abnormality apart from astereognosis in her right hand. Psychometric assessment showed mild deficits of left temporal function.

Patient 2. A 33-year-old woman developed focal seizures involving the right face at the age of 12. Her mother’s delivery had been prolonged, but milestones were normal. Possible risk factors were two falls, one from a bicycle at the age of 1 and the second at 8 years of age. Simple and complex partial seizures occurred weekly. Attacks lasted between 2 and 10 minutes, usually triggered by brushing her teeth on the left side and by eating. The seizures were highly stereotyped and characterized by twitching of the left corner of the mouth, jerky eye movements, and gritting of the teeth. Twice a year she had secondary generalization. She was treated with diazepam, carbamazepine, phenobarbital, gabapentin, and Chinese herbal medicines without benefit.

At the age of 24, 12 years after onset of her seizures, she developed left sided clumsiness and involuntary movements, initially limited to her fingers and several months later involving the whole left arm. These movements were choreoathetotic, associated with rigidity and dystonic posturing of the left upper and lower limbs. Her EEGs over the years showed epileptiform discharges over the right centromedial temporal regions. Her MRIs showed no abnormality.

At the age of 33 there was diffuse right hemispheric atrophy particularly involving the lower central area extending into the insula and infrasylvian region. There was marked atrophy of the right caudate nucleus and basal ganglia. An FDG PET study showed hypometabolism in the anterior right temporal and parietal regions. Hematologic and biochemical investigations were normal and there were no acanthocytes. She had a resection of the face area with considerable improvement of her seizures but with residual occasional mild twitching of the left face corner of the mouth, often when brushing her teeth. Histologic study revealed mild neuronal loss and gliosis in the gray matter and gliosis and perivascular lymphocytic infiltrations and focal collections of macrophages in the adjacent white matter. The blocks could not be relocated. She continued to receive treatment with carbamazepine and clonazepam. The choreoathetosis gradually diminished, but was still present 5 years later.

Patient 3. This 31-year-old right-handed woman had no antecedent or family history of epilepsy. She reached normal developmental milestones and completed a university degree in geography. There was no history of head injury, CNS infection, or febrile convulsions.

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The diagnosis of Rasmussen syndrome was entertained. Multiple antiepileptic drugs were used in an attempt to control seizures and IV Ig was prescribed monthly, but had no effect in the following 2 years. The patient underwent an en bloc right temporal lobectomy at age 36 years. Pathologic examination revealed histopathologic changes indicative of an encephalitic process consistent with Rasmussen encephalitis (RE). The patient remained seizure free for 3 months, but in the following 12 months she has experienced a gradual return of her seizures, which now occur almost daily but no limb paresis has developed.

Figure 1 Brain MRI of Patient 1

(A) Axial fluid-attenuated inversion recovery images showed an increased signal without swelling of the right temporal insular structures and of the right caudate nucleus. (B) Coronal IR images revealed a moderate dilatation of the head of the right caudate nucleus and the corpus striatum with dilatation of the horn of the right lateral ventricle (figure 1, C and D). In comparison with the previous MRI, a marked dilatation of the sylvian fissure and temporal horn and a much increased atrophy particularly involving the lower central area extending into the insula and infrasylvian region. There was marked atrophy of the right caudate nucleus and basal ganglia. An FDG PET study showed hypometabolism in the anterior right temporal and parietal regions. Hematologic and biochemical investigations were normal and there were no acanthocytes. She had a resection of the face area with considerable improvement of her seizures but with residual occasional mild twitching of the left face corner of the mouth, often when brushing her teeth. Histologic study revealed mild neuronal loss and gliosis in the gray matter and gliosis and perivascular lymphocytic infiltrations and focal collections of macrophages in the adjacent white matter. The blocks could not be relocated. She continues to receive treatment with carbamazepine and clonazepam. The choreoathetosis gradually diminished, but was still present 5 years later.

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Routine investigations were normal. The patient was found to be totally IgA deficient and without IgA antibodies. Serum and CSF virology was negative (with tests for herpes simplex virus type I, type II, varicella zoster virus, cytomegalovirus, Epstein Barr virus, and enterovirus RNA). VGKC antibodies titer was normal and tests for a wide range of other antibody tests negative. Her interictal EEGs showed excess slow activity over both temporal regions, greater on the left, and epileptiform discharges in the anterior and mid-temporal regions. Video telemetry indicated that her seizures were arising in the left frontal area with rapid propagation. An MRI of the brain showed initially mild atrophic changes on the left. Four years later there was progression of the atrophy, predominantly affecting the left frontal and temporal regions. Brain biopsy showed an inflammatory infiltrate with mainly B cells and no evidence of vasculitis. Immunohistochemistry showed sparse perivascular collection T cells (CD3 immunohistochemistry) and macrophages/microglia (CD68), which were also seen away from the blood wall (figure 2). The changes are not marked reflecting the mild nature of the case, and are compatible with RE.3

Treatment has included carbamazepine, lamotrigine, clonazepam, clobazam, gabapentin, levetracetam, topiramate, sodium valproate, and pregabalin but full seizure control has not been achieved. The patient is currently being treated with IVIg and prednisolone in addition to antiepileptic drugs.2 IVIg could be given and before each infusion, we checked for the presence of circulating IgA antibodies. Only if these were absent was IVIg administered. To date these have remained negative.

**DISCUSSION** Late onset or adult Rasmussen syndrome is usually less severe and tends to progress more slowly.3,4 It is also more likely to respond to immunologic treatment.5 The first patient is remarkable because of the onset with a movement disorder followed several years later by the appearance of seizures. The second patient had seizures, which remained focal for 12 years before the onset of choreoathetosis. The third patient had late onset refractory focal seizures without movement disorders. There was evidence for progressive tissue loss into the central area, caudate, and basal ganglia, strongly suggestive of RE.6-9 Recently, the presence of movement disorder in Rasmussen syndrome has been stressed by other authors,6,7 and it seems to correlate with atrophy of the caudate nucleus.7,4 Awareness of the possibility of movement disorder as a presenting symptom is important because it may lead to some confusion in the diagnosis, especially in the less common adolescent or adult patients.7 In all our patients the appearance of progressive atrophy on neuroimaging after a delay made the diagnosis of RE more likely. In none of these patients was there a marked progression of the condition over a number of years, nor the development of a marked fixed neurologic deficit (although mild signs were present) nor episodes of EPC or convulsive status epilepticus. These features are typical of Rasmussen syndrome and in their absence the diagnosis may be difficult to make. All three cases had typical MRI findings of progressive tissue loss and also histologic confirmation.

Adolescent and adult onset RE is well recognized.1 The patients reported here with onset during early adolescence or adult life are remarkable because of the circumscribed disease which does not lead to widespread involvement despite continuing epileptic activity and progressive focal atrophy. The tendency to occipital involvement in some of the reported adolescent or adult cases was also not a feature of these patients.

Clinical and laboratory features observed in our patients with a limited chronic focal form of RE are substantially different from those reported in VGKC-Ab-associated limbic encephalitis.10 In the latter, the mean age at diagnosis is 65 years, with most cases presenting over 40 years of age, and the typical presentation is with subacute onset of confusion, behavioral changes and psychosis, short-term memory loss, and seizures.10 The difference between our cases and patients with VGKC-Ab-associated limbic encephalitis is also reflected by the normal level of VGKC antibodies in antibodies in two patients tested.

In a previous report of a patient with late onset RE and dystonia,4 it was speculated that the movement disorder could have been related to epileptic activity in the hemisphere spreading to subcortical structures. This is rather unlikely at least in one of our patients, given the normality of repeated EEG and polygraphic studies for almost 3 years after appearance of the hyperkinetic movements. There is recent evidence of neuro-pathologically proven RE in which progressive unilateral motor deficit was present for several months without seizures.11 The atrophy of the caudate nuclei in our patients, observed also by other authors reporting patients with focal RE, is an important marker of this diagnosis although not specific.5,7,12 In particular the combination of...
movement disorder and focal epilepsy should arouse suspicion of the diagnosis.9

Finally, it is remarkable that the process appeared fairly localized in two of our patients over 20 years without proceeding to diffuse hemispheric atrophy. Although there are patients with RE who may remain stable for years after a focal resection and then develop spread of the disease, we believe that the patients presented here enlarge the spectrum of Rasmussen syndrome and confirm Dr. Rasmussen’s insightful suspicion of the existence of a more limited and less malignant form of the disorder.

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REFERENCES


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