Adult Rasmussen's Encephalitis

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Abstract

Introduction: Rasmussen's Encephalitis (RE) is defined by the presence of partial seizures associated to focal progressive cortical atrophy and -in advanced stages- hemiparesis, hemianopia and cognitive impairment, though it may appear focal neurological deficits at onset; and it's more prevalent in childhood. Approximately, 10% presents at adulthood. Because of its immunologic physiopathology, RE is considered autoimmune epilepsy. Treatment is focused on antiepileptic drugs (AEDs), steroids, intravenous immunoglobulins (IVIg) and immunosuppressant drugs.

A 37-year-old man presented to the Neurology department in 2015 with a history of epilepsy. Epilepsy began at age 13 with partial motor seizures. In 2011, he had a partial status epilepticus lasting 24 hours and then continued with multiple daily seizures. He had multiple AEDs schemes without good therapeutic response. At admission he had a frequency of 8 seizures in 2 hours. Electroencephalography (EEG), Video electroencephalography (VEEG) and brain magnetic resonance images (MRI) were performed. EEG and VEEG showed left and right partial motor seizures beginning at right frontal lobe. MRI showed mostly right frontal-temporal atrophy and mild involvement of left hemisphere, marking a progression in comparison with previous MRI studies. Cerebrospinal fluid (CSF) analysis indicated hyper proteinorachie, cell count and glucose level were normal. Oligoclonal bands, antineuronal antibodies, rheumatologic and infectious screening were normal. A neuropsychological evaluation was performed, showing mild cognitive impairment, with subcortical dysfunction. The patient received IVIg and there was a transient decrease of seizure frequency of 80%.

Conclusion: This case shows that RE is a progressive and chronic disease, with poor therapeutic response and drug-resistant seizures.

Keywords
Rasmussen's encephalitis, Partial status epilepticus, Drug-resistant autoimmune epilepsy

Introduction

Rasmussen's Encephalitis (RE) is a sporadic, severe cortical and subcortical disease-probably acquired- which is characterized by intractable motor seizures, mainly focal seizures, epilepsia partial continua (EPC) and progressive cognitive impairment with hemiparesis and language and cognitive disorders [1]. In 1958, Rasmussen et al described 3 patients suffering from focal seizures associated with localized chronic encephalitis [2]. It was first described in childhood and associated with viral encephalitis. Later, it was also described in adulthood and other possible etiologies were proposed. RE is a rare disease, and there are only 200 case reports analyzed in current literature. The median age of onset is 1-10 years and it is very infrequent in adolescence and adulthood [3]. There is no sex preference. A viral etiology was already suggested by Rasmussen based on the constituents of the immune reaction in the brains such as lymphocyte infiltration and microglial nodules [4]. However, so far all attempts to identify a pathogenic viral agent have been contradictory and inconclusive. Available data continue to suggest an immune basis to the pathogenesis of RE. Experiments on rabbits demonstrated that antibodies against glutamate/AMPA subunit 3 receptor (GluR3) provoked a clinical response similar to RE [5]. However, these antibodies were not found in all patients with RE; furthermore, anti-GluR3 was also found in other epileptic syndromes [6,7], though some of these reports are not well characterized [8]. Future antibody research in RE will probably concentrate on detecting possibly pathogenic antibodies other than anti-GluR3 [9,10]. A genetic origin has also been suggested, encephalopathy due to focal epilepsy or focal epilepsy due to focal immune response [11]. RE etiology remains unclear, though an immune basis with a role of humoral and cytotoxic response is the most accepted hypothesis.

Disease sets in otherwise healthy children with different types of seizures, especially partial motor seizures including EPC; usually starting in distal limbs. Later, seizures worsen, becoming more irregular and frequent, usually with postictal hemiplegia. In the next stage of the disease, well-stablished deficits appear, with progression over the course of RE. Finally, RE stabilizes with lower seizures but deficits remain [1,12,13].

A special mention is made about the setting of the disease in teenagers and young adults [14], though it has been also described in patients up to age 54 [15]. In this group of patients -which is supposed to represent 10% in some case series [3,16], the course of the disease is usually slower, with less damage and occipital lobe seizures [3]. Furthermore, very few cases of bilateral RE have been described [17,18], as well as others cases starting with hemiparesis and later epilepsy [19], or even cases with unilateral movement disorders, including hemiathetosis and hemidystonia [20].
According to brain biopsies and necropsies there are 4 different pathogenic patterns: group 1, earlier cases show an inflammatory pattern with numerous microglial nodules with or without neuronophagia, perivascular balloon cells and gliosis; group 2 is characterized by microglial nodules, perivascular balloon cells, and some portions of gyrual cortex with full necrosis; group 3, neuronal loss and gliosis with extensive perivascular balloon cells and some microglial nodules; and group 4, in late stages, shows few or none microglial nodules, neuronal loss and moderate perivascular inflammation combined with different degrees of gliosis [21]. It was demonstrated that perivascular balloon cells infiltrates were mostly T lymphocytes [22].

According to the 2005 European Consensus, a RE diagnosis can be made by fulfilling three criteria of part A, or two out of three criteria of part B. First, it must be evaluated part A, otherwise part B must be evaluated. Part A: 1. Focal seizures (with or without EPC) and unilateral cortical deficit, 2. EEG showing unihemispheric slowing with or without epileptiform activity and unilateral seizure onset, 3. unihemispheric focal cortical atrophy and at least one of the following: grey or white matter T2/FLAIR hyperintense signal, and hyperintense signal or atrophy of the ipsilateral caudate head. Part B: 1. Epilepsia partial continua or progressive unilateral cortical deficits, 2. progressive unihemispheric focal cortical atrophy, 3. T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astroglisis [14].

Evaluation through functional neuroimaging such as positron emission tomography (PET), single photon emission tomography (SPECT) or spectroscopy magnetic resonance imaging (sMRI) has been performed in diagnosis and follows up. Findings described are interictal hypoperfusion and hypometabolism, especially in rolandic cortex and numerous ictal hypometabolic foci. These findings correlate to worst outcome if they appear before structural abnormalities are seen in conventional MRI [23].

Up to date, there haven’t been found disease markers to confirm diagnosis. It has been proposed the detection of GlutR3- antibodies in serum but results are controversial [6]. CSF studies show in early stages an unspecified mild increase in proteins and cell count [24]; oligoclonal bands have been found in about 0-67% of patients [25-27].

Numerous treatments with AEDs have been unsuccessful in RE; only limited control on focal seizures and epilepsy partial continua in particular tends to be refractory to antiepileptic drugs. No AEDs alone or in combination show effectiveness. Of note, no data indicating higher efficacy of new AEDs in RE compared to the older ones. As a general rule, number and dose of AEDs should be kept as low as possible, one should try to abolish secondarily generalized tonic-clonic and, possibly, complex partial seizures; EPC, however, is almost never suppressed by AEDs and it provides little benefit to the patients if one tries to suppress this focal motor status epilepticus [28].

Since the first descriptions of the disease, surgery still remains as the most effective treatment for the seizures caused by RE. There have been many surgical approaches but the ones which have been more successful are those related to hemispherectomy - either anatomical or functional. In this respect, hemispherectomy and its modern variants have been found to be the so far and highly effective therapy to achieve seizure freedom. They have fewer complications than anatomical hemispherectomy and produce similar outcomes if they are well performed [29]. Most surgeries have stopped seizures in more than 70 per cent of patients [30,31].

Recently, there have been tried long-term treatments with corticosteroids [17,27,32], treatments with Intravenous Immunoglobulin (IVIG) [32], treatments with plasma-exchange or A protein immune adsorption [27] and Tacrolimus [33]. Only few patients have been treated with Rituximab as an alternative therapy in RE [34].

### Table 1: Lumbar puncion results. Blood glucose level 108 mg/dl.

<table>
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<th>CSF</th>
<th>Results</th>
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<td>Turbidity</td>
<td>Crystal clear</td>
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<tr>
<td>Color</td>
<td>Colorless</td>
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<tr>
<td>Glucose</td>
<td>50 (50% blood glucose level)</td>
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<tr>
<td>Total patients</td>
<td>298 mg/dl (NV 20-50)</td>
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<tr>
<td>Chloride</td>
<td>98 (NV 80-130)</td>
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<tr>
<td>White cell count</td>
<td>1 (up to 10)</td>
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### Case Report

A 37-year-old male patient who is derived from another Institution in 2015. No personal history is presented. His perinatal period as well as his neurologic development has been normal. He works as a private security agent.

History of the actual disease: His epilepsy began at the age of 13. The patient was initially treated with carbamazepine. He remained free of seizure activity for two years. Carbamazepine was prescribed until he was 17-year-old. At this age (1997) he was hospitalized for the increase in seizure frequency and a loading dose of phenytoin was administered. From age 17 to 33 he was treated with valproate, clonazepam, clobazam, topiramate, phenobarbital, phenytoin. As seizure frequency worsen medication dose needed to be adjusted with laboratory tests. He had left sided hemiparesis affecting his face (Todd’s phenomenon) and dysarthria for fifteen minutes. His medical history records (at the age of 16): sharp waves over the right frontal region. Continued left simple partial hemifacial seizures accompanied occasionally by unilateral weakness affecting arms and legs. He couldn’t recall having been free of seizure activity during this period. In 2008 at the age of 30 he underwent a MRI. In 2011 (aged 33) a new MRI was performed because of partial status epilepticus during approximately 24 hours. From 2011 to 2015; as an outpatient he was treated with multiple drugs: oxcarbazepine: 3600 mg/day, lorazepam: 5 mg/day and levetiracetam: 2000 mg/day. He continued to develop partial seizures. From 2011 onwards the seizure frequency increased to several times a day. In June 2015, on examination at the time of presentation, those seizures persisted without any clinical stability, 20 seizures/day so he was hospitalized. General physical examination was unremarkable except for a moderate dysarthria. VEEG showed: 8 seizures in 2 hours. Laboratory tests were completed (blood and CSF; table 1), VEEG and a new MRI. Routine lab parameters were normal. Antinuclear bodies were negative as well as ADNA, ANA, oligoclonal bands, HIV, PCR of HSV, CMV and EBV. Neurocognitive evaluation revealed a moderate subcortical dysfunction.

### Video EEG

Background rhythm during awake stage shows a theta rhythm, 5-6 Hz. Average amplitude, symmetric and synchronous in the posterior regions, it blocks with eye opening. Slow waves in the frontal regions during the entire study. Seizures last 60 seconds. They begin with rhythmic activity in left frontal region at 4 Hz (Figure 1A and Figure 1B), then 3 Hz and later 2 Hz (Figure 1A, Figure 1B and Figure 1C). The patient shows jerks first in the right cheek at a regular interval in 2-4 second, later right eyelid jerks are observed.

### Neuroimaging

**Figure 2, figure 3 and figure 4.**

### Treatment

Intravenous Immunoglobulin: 2 g/kg/day fractionized in 5 days, once a month during 5 months. VEEG control: 10 seizures in 4 hours: estimated 62.5% reduction within the ensuing three months after the cycles application; then seizures continued with the same frequency.

### Discussion

Rasmussen’s encephalitis is produced by chronic progressive inflammation of the brain, with infiltration of T lymphocytes into the brain parenchyma. This inflammation usually affects only one

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of atrophy and signal change. According to Video-EEG this patient has epilepsia partial continua and experiences myoclonus in left sided face, sometimes left leg and right eyelid. He doesn’t have a history of any disease related to CNS. The only explanation for the progressive is the persistence of partial motor seizures which would probably originate an autoimmune response that would in turn play a role in the perpetuation of seizures and therefore disease progress.

The findings of progressive brain atrophy and/or alterations of brain structure based on MRIs, particularly a MRI with gadolinium in a patient with EPC fulfilled the 2005 European consensus diagnosis criteria for the diagnosis of RE [14,36-39].

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and significant focal motor-cognitive decline. According to serial neuroimaging he fulfills part A criteria.

The increased protein found in CSF has low specific value because it may be seen in numerous inflammatory, infectious and neoplastic diseases.

The first line treatment proposed is immunotherapy: IV corticosteroids vs IVIG and tacrolimus. This treatment delays surgery, as it has been established the only curative treatment of RE. Other options are plasma-exchange, natalizumab, azathioprine and AEDs. Long-term treatment with IVIG may be useful, probably to modify the course of the disease and must be considered prior to surgery [40]. Though surgery is curative, its adverse effects are significant, such as functional deficits. In patients that reached the final stage of RE with minimal functional capacity of the affected hemisphere, surgery is a valid option, especially when seizures became intractable. Corticosteroid therapy results are variable. In a study, the type of epilepsy and motor and cognitive outcome were evaluated in 49 patients of age 8.7 ± 10.5 with RE, who were treated with immunotherapy: IVIG at 100 mg/kg/day, methylprednisolone at 30 mg/kg/day for three days and tacrolimus at initial dose of 0.1 mg/kg/day; compared to functional hemispherectomy. The results were: seizure freedom in 23% with IVIG therapy, 81% with methylprednisolone, 42% with tacrolimus and 71% with surgery. The > 80 intelligence quotients (IQs) were: 43% with IVIG, 50% with corticosteroids, 29% tacrolimus and 0 % with surgery. Only patients treated with immunotherapy showed motor improvement. Hemispherectomy worsened the motor functions in all patients; compared with worsened motor function of 62% of IVIG and 10% of steroids [41,42]. The study made by Bien et al about tacrolimus vs. IVIG showed that both treatments may delay tissue loss and functional deterioration in patients with RE [42].

Plasma-exchange is a useful adjuvant therapy in patients with RE, specifically in those with status epilepticus before surgical removal [11].

Our patient received 5 monthly cycles of IVIG, and there were no modifications in his antiepileptic treatment. The was an estimated seizure reduction of 62.5% during the three months after IVIG therapy. However, after this time, seizures continued with the initial frequency. This patient was not a good candidate for surgery because he had both hemispheres compromised, especially the right lobe and he was right-hand, and it would worsen his quality of life and outcome.

Conclusion
This case of adult RE shows a chronic, progressive disease with drug-resistant seizures. The disease went on a prolonged course compared with children onset, and it had fewer structural lesions. Though RE outcome depends on the underlying etiology, in this case the seizure frequency worsened the course of the disease.

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References


