CASO CLÍNICO/CASE REPORT

Adult-Onset Rasmussen's Encephalitis: Response After Steroid Pulses

Encefalite de Rasmussen de Início Adulto: Resposta Após Pulsos de Esteróides

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Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 20, Número 1, janeiro-março 2020. Versão eletrónica em www.sinapse.pt
Case Report, published in Sinapse, Volume 20, Number 1, january-march 2020. *Electronic version in www.sinapse.pt*

Keywords:
Encephalitis/diagnosis; Encephalitis/therapy; Epilepsia Partialis Continua.

Palavras-chave:
Encefalite/diagnóstico; Encefalite/tratamento; Epilepsia Partialis Continua.

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Recebido / Received: *2019-07-01*
Aceite / Accepted: *2019-12-09*
Publicado / Published: *2020-06-30*

DOI: 10.46531/sinapse/CC/190016/2020

Abstract

Introduction: Rasmussen's encephalitis (RE) is an infrequent chronic neurological disorder characterized by unihemispheric inflammation of the brain cortex, refractory epilepsy, and progressive motor and cognitive decline. The presentation in adulthood is uncommon and represents around 10% of the cases.

Case Report: A 54-year-old woman developed focal myoclonic seizures involving the right face and upper limb. The seizures were recurrent and progressed to *Epilepsia partialis continua*. Gradually, she developed cognitive impairment. The magnetic resonance imaging showed left unihemispheric frontoparietal moderate atrophy compared to the baseline magnetic resonance imaging. Rasmussen's encephalitis was diagnosed according to the Bien criteria. The antiepileptic drug combination treatment partially controlled the seizures. After pulses of methylprednisolone, the patient was discharged seizure-free.

Conclusion: Rasmussen's encephalitis is rare in adults; however, it should be considered as a differential diagnosis in patients with a history of pharmacoresistant focal seizures with progressive involvement of higher functions and imaging studies showing cerebral hemiatrophy. Current pharmacological treatment for this condition does not include the use of steroids. Nevertheless, in this case, methylprednisolone represented a treatment option in a limited-resource context.

Resumo

Introdução: A encefalite de Rasmussen (ER) é uma doença neurológica crónica pouco frequente, caracterizada por inflamação unihemisférica do córtex cerebral, epilepsia refratária e declínio motor e cognitivo progressivo. A apresentação na idade adulta é incomum e representa cerca de 10% dos casos.

Caso Clínico: Uma mulher de 54 anos desenvolveu convulsões mioclónicas focais envolvendo a face direita e o membro superior. As crises foram recorrentes e evoluíram para *epilepsia partialis continua*. Gradualmente, a doente desenvolveu comprometimento cognitivo. A ressonância magnética mostrou atrofia frontoparietal unihemisférica moderada em comparação com a ressonância magnética basal. A encefalite de Rasmussen foi diagnosticada de acordo com os critérios de Bien. O tratamento combinado com fármacos antiepilépticos controlou parcialmente as

convulsões. Após tratamento com metilprednisolona injetável aplicada sequencialmente a paciente recebeu alta sem convulsões.

Conclusão: A encefalite de Rasmussen é rara em adultos; no entanto, deve ser considerado como diagnóstico diferencial em pacientes com histórico de crises focais farmacorresistentes com envolvimento progressivo de funções cognitivas e estudos de imagem mostrando hemiatrofia cerebral. O tratamento farmacológico atual para essa condição não inclui o uso de esteróides. No entanto, neste caso, a metilprednisolona representou uma opção de tratamento num contexto de recursos limitados.

Introduction

Rasmussen's encephalitis (RE) is a rare chronic cerebral disease, characterized by unilateral cortical inflammation, drug-resistant epilepsy, and progressive cognitive and motor impairment.[1] RE affects mainly pediatric population, while adolescence or adult-onset is very rare (<10%).[2]

Worldwide epidemiological data about Rasmussen disease is scarce. The estimated incidence in Europe ranges from 1.7 to 2.4 cases per 10 million inhabitants, without differences among gender, age or ethnicity.[3,4] In Latin-America, the data is limited to case reports and series.[5,6]

The pathophysiology is not yet fully known. It is clear that there is an inflammatory response mediated by T lymphocytes, initially T-helpers, involved in autoimmunity, which would explain the permanent inflammation, the presence of circulating anti-neural antibodies and the destruction of the brain parenchyma.[7] Adult-onset RE does not reach the criteria for autoimmune encephalitis (<30%) and specific autoimmune biomarkers are still missing.[8] Nevertheless, autoantibodies against glutamate receptors, AMPAR and Munc-18-1 could be found in classic RE.[9]

The onset is marked by focal to bilateral seizures that might progress to *epilepsia partialis continua* (EPC) in half of the patients. Additionally, there are encephalitic symptoms such as irritability, emotional lability, and hyperactivity. Over the course of the disease, the hemiparesis and neurological deficits establish, while the frequency of the seizures arises. These, are resistant to medical treatment, and partial epileptic status may appear.[1,10] The most effective treatment in the pediatric presentation is surgery, and the results are favorable.[11]

The diagnostic criteria for RE were established by Bien *et al* in the "European Consensus Statement" (81% sensitivity and 92% specificity.[12] They were reviewed and modified by Olson *et al*[13] (**Table 1**).

Table 1. The Bien Diagnostic criteria for Rasmussen's encephalitis modified by Olson.

PART A	**3/3 REQUIRED**
1.- Clinical	Focal seizures (with or without epilepsia partialis continua) and Unilateral cortical deficit(s).
2.- EEG	Unihemispheric slowing with or without epileptiform activity and Unilateral seizure onset
3.- MRI	Unihemispheric focal cortical atrophy and at least one of the following: - Grey or white matter T2/FLAIR hyperintense signal - Hyperintense signal or atrophy of the ipsilateral caudate head
PART B	**2/3 REQUIRED**
1.- Clinical	*Epilepsia partialis continua* or progressive° unilateral cortical deficit(s)
2.- MRI	Progressive° unihemispheric focal cortical atrophy
3.- Histopathology	T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages, B cells or plasma cells or viral inclusion bodies exclude the diagnosis of RE.
ADDITIONAL	Item 3 of Part B plus 2 Items of part A

Progressive ° = at least two clinical or imaging tests suggest the presence of the entity, each separated by six months.

Legend: The diagnostic criteria for Rasmussen's encephalitis were first stablished by Bien *et al* at the European consensus statement for RE in 2005. In 2013, Olson *et al* included an additional criterion.

Adult-onset Rasmussen's encephalitis represents less than 10% of the total cases. The presentation is less aggressive and progressive, while the diagnosis is challenging since the classic criteria are hardly reached.[8]

We report the case of adult-onset RE according to the diagnostic criteria, which exemplify the diagnostic and therapeutic challenges, and the potential use of steroid pulses in a limited-resource context.

Case Report

In 2013, a previously healthy 54-year-old right-handed woman, from Callao, Peru, developed involuntary movements of the right arm. She went to a local hospital and received treatment with benzodiazepines, which she quit over undetermined time. In 2015, she came to our neurology department with myoclonic seizures in the right face and ipsilateral upper limb. The seizures were focal, without loss of consciousness, last five to ten seconds and repeated 30 to 40 times per day. At the neurological examination, loss of muscular She was performed an electroencephalogram (EEG); however, it was not conclusive. In the cerebrospinal fluid (CSF) exam, the cytochemical study did not show any alterations. The adenosine deaminase profile (ADA) was between normal ranges; the Gram stain, the India ink stain was negative as so was the ANCA and ANA profile. After this results, we excluded the possibility for infectious diseases or systemic autoimmune. Therefore, she was diagnosed with hemiclonic epilepsy and started on antiepileptic drug combination therapy, responding with partial control of the seizures. Nevertheless, three months later she progressed to focal status epilepticus, it was refractory to midazolam but responded to IV phenytoin. She was discharged home with a new combination of drugs that could not control the seizures completely either. A year after this episode, the family reported she gradually developed progressive memory loss and behavioral alterations. The neuropsychological assessment reported moderate cognitive impairment, difficulties in the executive functions of conceptual modality (calculation and abstraction), and attention to visual stimuli and deferred audio-verbal memory. By this point, epilepsy had become refractory.

Brain magnetic resonance imaging (MRI) shows cortico-subcortical atrophy with a left frontotemporal predominance, in addition to basal ganglia hyperintensity in T2 / FLAIR. The patient had a previous MRI from 2013, which showed no signs of inflammation or lesions. In a control interictal non-video EEG that lasted 45 minutes, there were evident alteration such as left frontocentral slowing, epileptiform activity in frontal and left temporal regions and spikes in derivations FP1, F7, T3, T5 (**Fig. 1**). There were no other findings in the rest of derivations.

During the disease, she was prescribed a combined antiepileptic drug treatment as follows: Levetiracetam (1500 mg b.i.d.), lamotrigine (100 mg b.i.d), lacosamide (100 mg b.i.d.), and clonazepam (4 mg b.i.d.). Despite the efforts, the seizures remained refractory.

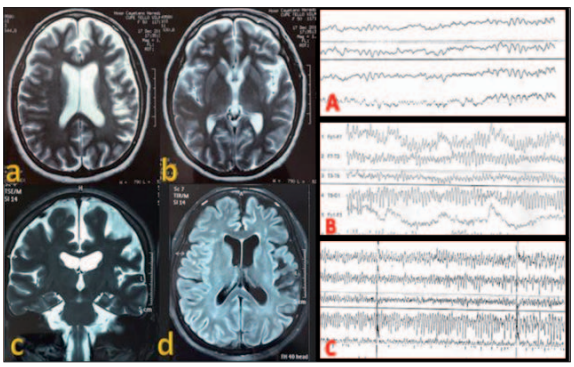

Figure 1. Radiological and electrophysiological features.

On the left, the MRI shows: (a) T2 axial incidence, there is atrophy of the left hemisphere (b) cortical atrophy of the left hemisphere, with a predominance in the temporal and frontal peri-insular region. (c) T2 coronal incidence, the previously described atrophy conditions discrete enlargement of the left lateral ventricle. (d) T2/FLAIR, hyperintensity in left basal nuclei. On the right, the EEG shows: (A) left frontocentral slowing, (B) epileptiform activity in frontal and left temporal regions and (C) spikes in derivations FP1, F7, T3, T5.

In August 2017, the patient had a focal status epilepticus which responded to midazolam; however, she was readmitted for the same cause four months later. In the later episode the treatment with midazolam failed, so she was started on pulses of methylprednisolone. The result was remarkable; therefore, she was programmed for monthly pulses of methylprednisolone for three days, at 1 g per day. After the pulses, the patient remained completely seizure-free and the cognitive neuropsychological assessments were normal at the moment of discharge. A timeline of the course of the disease and the approach could be seen in **Fig. 2**.

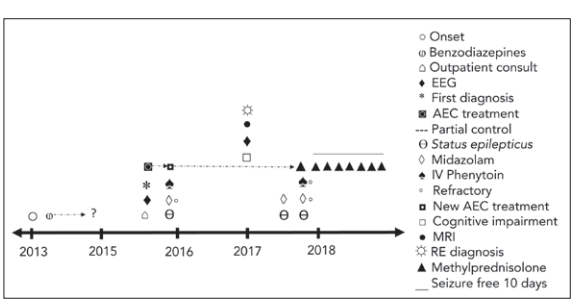

Figure 2. Timeline of disease course and approach.

This timeline shows the evolution of the disease and the treatment administered in each moment, since the onset of the symptoms and the first medical prescription, through every relapse, until the last pulse of methylprednisolone at discharge. AEC: Antiepileptic drug combined treatment.

Diagnosis according to the criteria

The patient fulfilled the 3/3 items of part A (clinical,

EEG and MRI), for the diagnosis of Rasmussen encephalitis, established by Bien *et al* and modified by Olsen.[12,13] We did not perform a brain biopsy, because of the patient and her family decision.

Discussion

The patient met the diagnostic criteria proposed by Bien *et al*, which included: focal seizures and unilateral cortical deficit, EEG alterations and progressive unihemispheric atrophy in MRI. Cognitive deterioration was slow, as well as the appearance of the hyperintensity in basal nuclei in T2 / FLAIR, characteristics of adult RE.

ER is a rare entity, with low prevalence and incidence rates and even indirectly calculated through case series reports. In addition to this, the adult presentation is rarer, as the case of our patient, being recognized in only 10% of the cases mainly a pediatric disease.

In addition, the ER of the adult does not always fulfill all the classic criteria, especially with the hyperintensity in T2 / FLAIR. The pathognomonic radiological images are not always presented in the adult as described in the child, these could even be bilateral or accompanied by cortical dysplasia and the time of appearance in the MRI is variable.[14] As in the case of our patient, the delayed of the appearance of the image last around two years; as well as the hemispheric atrophy progressed slowly.

There had been described that most of the late-onset patient fulfill part B criteria, which requires long-term follow-up (up to 77%). This explains the lateness in diagnosis in this age group.[8] We follow our patient for more than a year until the diagnosis; she exhibited symptoms that satisfied the criteria which characterized this presentation of the disease: i) classical focal lobe epilepsy evolving into multifocal epilepsy, ii) delayed occurrence of neurological impairment and iii) delayed focal cortical atrophy.[8]

Regarding the immunological evaluation in our case, we could not perform a comprehensive laboratory exploration due to the not availability of these tests in the Peruvian public health system. However, we suggest for future similar cases to test the anti-GAD and anti-VGKC titles as previous cases reported.[5,6]

Seizures were refractory to conventional treatment and combined AED. Despite the clinical presentation, motor and cognitive impairment are much less disabling and progressive than the expected in pediatric disease. This pattern was previously described.[1] Additionally, Gambardella *et al* reports in a series of three cases of female patients, with a mean age at diagnosis of 33 years, who present a variant of the disease characterized by focal seizures but without the classic progressive motor deficit, a phenotype called by the author as limited focal chronic encephalitis, who responded well to immunotherapy,[15] similar characteristics presented in our patient.

Kupila *et al* reported a case of adult RE, with biopsy-confirmed diagnosis, who developed unilateral focal onset seizures, which progressed to EPC; improved with intravenous immunoglobulin (IVIG), fosphenytoin, and methylprednisolone administration. The patient remained seizure-free for three years (time of publication) with AED combined treatment, oral prednisone and monthly pulses of IVIG.[16] Poloni *et al* reported the case of a 29-year-old patient with RE, who meets the diagnostic criteria of Bien *et al*, with polymorphic crises (focal, motor and sensory), with infection screening tests negative, who improved with courses of methylprednisolone. However, three years later, he presented hemiparesis, cognitive symptoms, and depression, and a CSF examination suggestive of CMV infection, which when treated with high-dose intravenous polyvalent immunoglobulins (HDIV), achieved remarkable improvement. He underwent twelve HDIV courses in the following four years in addition to treatment with control antiepileptic drugs, with remission of symptoms that he maintained during follow-up for 15 years.[17] For that, we are currently doing a follow up of our patient to detect earlier changes in the neurological status and start other immunomodulatory therapies if she needs it. The initial administration of methylprednisolone in this patient was mainly because IVIG is not available in the Peruvian public health system due to their high cost.

The treatment in adults is mainly medical and palliative. Unlike the pediatric presentation, most adult patients probably will not benefit from total hemispherectomy, unless seizures represent a vital risk. Varadakar *et al* suggest considering the seizures as an axis for deciding the approach.[1] To enhance the outcome of medical treatment on seizures, the adjuvant uses of immunomodulatory therapy has been tested.[8] In the case of our patient, epileptic focal and myoclonic seizures were disabling, therefore treatment with antiepileptic drugs was started, trying the best possible combination with the greatest therapeutic effect and fewest side effects. Currently, treatment with monthly methylprednisolone

pulses, achieved partial remission of the seizures, entitling our patient functionality and independence. ■

Acknowledgments/Agradecimentos: We have to express our appreciation to the Neurology department of the "Daniel Alcides Carrion" National Hospital for sharing their location in the aim of knowledge.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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