Journal of Epilepsy and Clinical Neurophysiology

J Epilepsy Clin Neurophysiol 2010;16(2):59-63

Rasmussen Encephalitis: Longterm Outcome after Surgery*

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ABSTRACT

Background and Purpose: Rasmussen Encephalitis (RE) is characterized by intractable epilepsy, progressive hemiparesis and unilateral hemispheric atrophy. The progression of the symptoms usually occurs within months to few years. Antiepileptic drugs are usually not effective to control disease progression and epilepsy surgery in the form of hemispheric disconnection has been considered the treatment of choice. This work describes the clinical and electrographic analyses, as well as the post-operative evolution of patients with RE. **Patients and Methods:** This work includes all the patients with RE evaluated from January 1995 to January 2008 by the Ribeirão Preto Epilepsy Surgery Program (CIREP) considering demographic data, interictal and ictal electroencephalographic (EEG) findings; anatomo-pathological findings and clinical outcome. **Results:** Twenty-five patients were evaluated, thirteen were female. Mean age of epilepsy onset was 4.4±2.0 years. There were no differences between patients with slow and fast evolution with respect to age of epilepsy onset (p=0.79), age at surgery (p=0.24), duration of epilepsy (0.06), and follow-up (p=0.40). There were no correlations between the presence of bilateral EEG abnormalities or the absence of spikes and post-operative seizure outcome (p=0.06). Twenty-three patients underwent surgery. The mean follow-up was 75.3 months. Eleven patients had total seizure control. Twelve individuals persisted with seizures consisting of mild facial jerks (6 patients), occasional hemigeneralized tonic-clonic seizures (3 patients), and frequent tonic-clonic seizures (3 patients). Mental and language impairment was observed in 15 and 12 patients, after surgery, respectively. **Conclusions:** This retrospective study reported the clinical and electrographic analysis, as well as the evolution of 23 patients with RE. Fourteen patients achieved satisfactory seizure control, three patients had partial response to surgery, and five patients had maintenance of the pre-operative condition. All patients with left side involvement presented with some language and cognitive disturbance.

Keywords: Rasmussen encephalitis; intractable epilepsy; pediatric population and epilepsy surgery.

RESUMO

Encefalite de Rasmussen: avaliação de resultados depois da cirurgia

Introdução e Objetivos: A Encefalite de Rasmussen (ER) é caracterizada por epilepsia intratável, hemiparesia progressiva e atrofia hemisférica unilateral. A progressão dos sintomas geralmente ocorre em meses ou poucos anos. As drogas antiepilépticas são usualmente ineficazes no controle da progressão da doença e o tratamento cirúrgico, com desconexão hemisférica tem sido considerado o tratamento de escolha. Neste trabalho descreveremos os achados clínicos e eletrográficos, assim como a evolução pós-operatória de pacientes com ER. **Pacientes e Métodos:** foram incluídos todos os pacientes com ER avaliados no período de janeiro de 1995 a janeiro de 2008, no Centro de Cirurgia de Epilepsia de Ribeirão Preto (CIREP), sendo considerados os dados demográficos, os achados do eletrencefalograma (EEG) interictal e ictal, resultado anatomo-patológico e o seguimento clínico. **Resultados:** Vinte e cinco pacientes foram avaliados, 13 eram do sexo feminino. A idade média de início da

* Trabalho premiado Prêmio Paulo Niemeyer durante o XXXIII Congresso Brasileiro de Epilepsia/LBE, 03-06 junho 2010 (Brasília/DF).

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Received Apr. 28, 2010; accepted June 03, 2010.

epilepsia foi de 4.4±2.0 anos. Não houve diferenças significativas entre os pacientes com evolução lenta ou rápida considerando-se a idade de início da epilepsia (p=0,79), idade da cirurgia (p=0,24), duração da epilepsia (p=0,06) e tempo de seguimento (p=0,40). Não houve correlação entre a presença de alterações bilaterais ou ausência de descargas ao EEG e o seguimento pós-operatório (p=0,06). Vinte e três pacientes foram submetidos à cirurgia. O tempo médio de seguimento foi de 75,3 meses. Onze pacientes evoluíram com controle total das crises. Doze pacientes permaneceram com crises que consistiram de clonias faciais sutis (6 pacientes), crises tônico-clônicas hemigeneralizadas ocasionais (3 pacientes) ou crises tônico-clônicas frequentes (3 pacientes). Alterações cognitivas e de linguagem foram observadas em 15 e 12 pacientes após a cirurgia, respectivamente. **Conclusões:** este estudo retrospectivo relatou os achados clínicos, eletrográficos e a evolução de 23 pacientes. Controle satisfatório das crises foi obtido em 14 pacientes. Três pacientes tiveram resposta parcial com a cirurgia e cinco pacientes mantiveram o quadro pré-operatório. Todos os pacientes com envolvimento do hemisfério cerebral esquerdo evoluíram com distúrbio de linguagem e cognitivo.

Unitermos: Encefalite de Rasmussen; epilepsia intratável; população pediátrica e cirurgia de epilepsia.

INTRODUCTION

Rasmussen Encephalitis (RE) is a rare devastating childhood disease characterized by intractable epilepsy, frequently accompanied by epilepsia partialis continua, progressive hemiparesis and unilateral hemispheric atrophy.[1] During evolution, seizures usually become continuous and ipsilateral hemiparesis occurs. The progression of the symptoms to significant neurological impairment usually occurs within months to few years.[17] Although RE causes are unkown, an autoimmune process has been suggested[2,9,12,16] and surgery is the treatment of choice to try to avoid mental retardation, dementia and death.[1]

Electroencephalographic usually show a pattern of recurrent seizures, with activity over the central motor area.[3,4] Neuropathology characteristically shows cortical abnormalities consisting mainly of microglial nodules, perivascular lymphocytic cuffing and neuronophagy.[7,17]

In this study, we have reviewed the clinical, electrographic and post-operative evolution of patients with RE, considering long-term prognosis.

PATIENTS AND METHODS

Patients' selection

All patients with RE evaluated from January 1995 to July 2008 in our center were included. Patients were followed as part of the Ribeirão Preto Epilepsy Surgery Program (CIREP) using standardized protocols previously published and approved by the Ethics Committee of our institution. All individuals had medically intractable epilepsy.

Methodology

Patients' evaluation included a detailed clinical history and neurological examination, interictal scalp EEG, interictal and ictal video-EEG monitoring, structural and functional imaging and neuropsychological testing. Neuroimaging workup included high resolution 1.5 T Siemens Vision MRI, as well as multiple ictal and interictal SPECT scans. Neuropsychological testing was performed whenever possible (all cases, except for those patients with profound mental retardation or severe behavioral problems).

Demographic variables analyzed were: gender; age at epilepsy onset; seizure semiology; seizure frequency; interictal and ictal EEG findings; age at surgery, when done; duration of epilepsy; surgery complications; follow-up duration, anatomo-pathological findings; post-surgery outcome; and AED treatment after surgery. Patients were divided into two groups, according to the neurological progression of the disease: fast evolution – patients with rapid hemiparesis installation, and slow evolution – patients that developed hemiparesis more than one year after seizure onset or individuals who developed mild hemiparesis or language disturbance only.

Postoperative seizure status was obtained on follow-up visits with the medical staff. Whenever this information was not available or considered unclear, the patient or a close relative was contacted by telephone. Post-surgical AED therapy was kept unchanged for at least two years in patients with monotherapy. In the case of individuals on polytherapy, dosages were reduced or converted to monotherapy whenever possible.

Statistical analysis

Categorical variables were analyzed by Chi square's or Fisher's exact tests. Continuous variables were analyzed by Student's t test or the Mann-Whitney U test, and significance level was considered at $p<0.05$. All tests were performed using the SSPS 13 statistical program.

RESULTS

Twenty-five patients with RE evaluated in our center were analyzed. The main characteristics of this group of

children and adolescents are resumed in Table 1. Twelve patients (48%) were female. The youngest child in the group was aged two years and the oldest, 14 years (mean: 7.8±3.5 years).

Table 1. Demographic data.

Data	Number of cases
Sex	13M / 12F
Side involved	11Left / 14Right
Evolution	14 fast / 11 slow
Epilepsia partialis continua	25 Yes
Surgery	16 Functional hemispherectomy 3 Anatomical hemispherectomy 1 Hemidecortication 3 focal resections

The mean age at epilepsy onset was 5.6±2.2 years and duration of epilepsy had a mean of 2.6±2.4 years. Twenty-four patients had *epilepsia partialis continua* at the time of evaluation and one patient had focal motor seizures. Two patients also had tonic seizures. Slow evolution was observed in 11 patients and fast evolution in 14. There were no differences between patients with slow and fast evolution in terms of age of epilepsy onset (p=0.79), age at surgery (p=0.24), duration of epilepsy (0.06) and follow-up (p=0.40).

Ictal EEG evaluation revealed unilateral onset in 19 patients and bilateral or contralateral onset in six patients. This finding was not statistically significant when compared for long-term seizure outcome (p=0.06).

Immunoglobulin therapy was tried in 12 patients (one to seven applications, dose 1.2g per kilo). Two patients were also submitted to plasmaferesis, three patients to corticosteroids therapy and one to immunosupression with tacrolinus. All patients showed transiet response in respect of seizure control.

Twenty-three patients underwent surgery: 20 patients were submitted to hemispheric surgery (16 functional hemispherectomy, 3 hemispherectomy and 1 hemidecortication), while only three patients had partial surgeries (one patient was submitted to peri-sylvian resection, one to temporal resection and one patient underwent frontal lobectomy for diagnosis purpose only). The surgical specimens revealed varied degree of typical RE findings that consisted of microglial nodules, perivascular lymphocitic infiltrate, neuronophagia and gliosis.

The mean follow-up was 75.3 months (±43.9 months), ranging from 18 to 165 months. No outcome differences were observed between gender (p=0.39) or when the evolution of neurological deficits was considered (fast x slow evolution, p=0.50). From the 20 patients submitted to hemispheric surgery, eleven patients had total seizure control and nine persisted with seizures that consisted in mild facial jerks (six patients), occasional hemigeneralized tonic-clonic seizures (two patients), and frequent tonic-clonic seizures (one patient). Two patients with partial surgery persisted with frequent seizures and the other one persisted with continuous facial jerks. Considering the three patients with the worst outcome, one patient had seizure recurrence four years after surgery, one after AED were dropped out by parents one month after surgery, and two patients died during follow-up of pneumonia and sepsis.

AED were reduced in 56.6% of the patients and maintained in 11.8% of the cases. In 31.6% of the patients, AED had to be increased after surgery.

All the patients had normal neurological and cognitive development before epilepsy onset. Throughout evolution, 19 patients (76%) developed contralateral hemiparesis. Mental impairment was observed in 15 patients (60%) before surgery, which was mild in 10, moderate in three and severe in two. Aphasia was present in 12 patients (48%). One patient was under continuous intensive therapy care and could not be evaluated for motor and language deficits before surgery.

After surgery all 20 patients submitted to hemispheric surgery had worsening of the neurological deficits with complete hemiplegy and hemianopsy. According to neuropsychological tests, ten patients (50%) did not have any cognitive modification, eight patients (40%) had cognitive decline, and only two patients (10%) had cognitive improvement. Considering language dysfunctions, 40.9% of the patients were aphasic. Comparing pre- and post-operative language deficits, all the patients that had pre-operative normal language persisted with normal language after surgery, irrespective of the surgery side. From the 12 patients with language disturbance, four patients (33.3%) improved, three patients (25%) had their conditions worsened, and five patients (41.7%) did not have any changes in language expression. In summary, 66.76% of the patients did not improve language expression after surgery. Two patients were not operated on because of slow evolution of the disease and abscence of motor deficits.

DISCUSSION

This retrospective study reports the clinical and the electrographic analysis, as well as the evolution of 25 patients with RE. Almost all the patients presented to us with epilepsia partialis continua and hemiparesis. In this context, surgical procedure may be the better approach to achieve seizure control. Hemispheric disconnection is the surgery of choice,[20] although partial resections were done in patients with normal motor skills. In almost half of the cases treatment with immunomodulatory drugs were tried, but we did not observe a persistent response. After a mean of five applications patients returned to epilepsia partialis continua situation and motor deficit were installed.

Seizure and cognitive outcome is controversial in most of the RE series.[11,21] In our series, 14 patients achieved satisfactory seizure control, three patients had partial response to surgery, and five patients had maintenance of the pre-operative condition. From this series, two patients died during follow-up, suggesting that the long-term evolution of patients whose seizures cannot be stopped or attenuated may be devastating. Bilateral EEG abnormalities were observed in other series of patients with major hemispheric lesions,[8] and it was suggested that seizure relapse was more related to etiology than to the EEG abnormalities, so that interictal lateralized EEG may be sufficient to determine the unihemispheric involvement in seizure onset. Carmant et al.[5] data stressed that the absence of an independent ictal onset in the contralateral hemisphere should be sufficient to lateralize seizures in patients with hemispheric lesions.

An interesting point is language evolution in patients with left side involvement. Although no specific tests to determine language dominance were performed by us, all the patients with left side involvement presented with some language disturbance that did not improve after surgery in 66.6% of the patients. Also, cognitive evaluation showed that the majority of the patients did not have significant improvement, while 38.1% had cognitive deterioration after surgery. These data suggest that language and cognitive outcome is critical even in younger patients.

Curtiss and Bode[6] evaluated language outcome following hemispherectomy in children with epilepsy and found that patients with RE had the best linguistic outcome, which was not influenced by age of epilepsy onset or age at surgery. Isolated cases of language function recovery in patients submitted to hemispherectomy in late childhood have been described,[10,14,19] suggesting that language reorganization may occur in some patients after a long follow-up. We did not observe any improvement even in patients evaluated one year after surgery. Maehara et al.[15] observed a better speech function in patients who had spoken preoperatively, but the great majority of patients who did not develop language before surgery were able to speak only single words, suggesting that language recovery is not only influenced by age at surgery, but also by developmental skills. A significantly worse outcome in both receptive and expressive language was observed by Pulsifer et al.[18] in patients with left hemispherectomy. These authors also observed that after five years of follow-up, patients with RE did not have a significant change in general intelligence, receptive language, behavior and adaptative functioning, but expressive language scores were on average lower compared with those observed before surgery.

Cognitive improvement has been analyzed in patients submitted to hemispherectomy, and the outcome does not seem to be as positive as the epileptic outcome.[13] Also, a substantial decline in the intelligence coefficient is most likely in patients with RE and an initial high-functioning baseline.[18] Nevertheless, the usual outcome of the disease without surgery is always dismal.

In conclusion, RE treatment with immunomodulatory therapy seens to have transient response in respect to seizure control and reduction of motor deficit development. Patients submitted to hemispheric surgery had a good outcome in terms of seizure control. Cognition, as well as the receptive and expressive language is usually impaired, especially in patients whose lesion is located in the left hemisphere. A more detailed approach for evaluation of the cognitive and language skills needs to be developed so that a better measure of post-operative impairment can be achieved.

ACKNOWLEDGEMENT

The authors thank the epilepsy fellows, neurology residents, and staff of the Epilepsy Outpatient Clinics and Video-EEG Monitoring Unit of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto/USP. This work was supported by FAPESP, CNPq, and FAEPA.

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