Rasmussen Encephalitis

A Clinicopathologic and Immunohistochemical Study of Seven Patients

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Key Words: Rasmussen encephalitis; Epilepsy; Chronic encephalitis; Epstein-Barr virus

Abstract

We retrospectively reviewed the clinicopathologic features and immunohistochemical profiles of 7 patients with Rasmussen encephalitis (age range, 3.5-15 years at surgery). All had medically intractable seizures (6 months' to 7 years' duration); all but 1 developed unilateral hemiparesis. Histologically, all cases were characterized by leptomeningeal and parenchymal perivascular chronic inflammation consisting primarily of T lymphocytes (CD3+, CD5+, CD7+). In all but 1 case, a predominance of CD8+ T-cytotoxic/suppressor lymphoid cells over CD4+ cells was observed. All cases had rare B lymphocytes (CD79a+, CD20+). Rare CD10+ and no CD56+ cells were noted. All cases were marked by diffuse proliferation of microglial cells, highlighted on CD68 immunostaining. Focal microglial nodule formations were observed in 4 cases and focal cortical atrophy in 5 cases. Viral inclusions were not noted. There was no evidence of Epstein-Barr virus by LMP-1 antibody immunostaining. The histologic findings of Rasmussen encephalitis resemble those of viral meningoencephalitis. The pathologic findings may be only focally present, and missed, if diagnosis is made or confirmed with biopsy alone. Most lymphoid cells have a T-cell immunophenotype, with a predominance of CD8+ cells in most cases.

Rasmussen encephalitis is a syndrome marked by chronic encephalitis and medically intractable focal epilepsy, initially reported in 1958 by Rasmussen et al.[1] The initial report described 3 pediatric patients who had severe epilepsy with slowly progressive, unilateral neurologic deterioration. Histologically, the lesions were marked by pathologic features typically associated with viral encephalitis, including widespread perivascular chronic inflammation and microglial nodule formation. Although much has been written about the entity, the precise etiology still remains unknown.

We reviewed the clinicopathologic features of 7 patients with Rasmussen encephalitis. Particular attention was given to the immunohistochemical profile of the inflammatory cells observed in this process, about which there is relatively little detail in the literature.

Materials and Methods

The pathology files were searched for cases of patients diagnosed with Rasmussen encephalitis during a 10-year period (May 1991 through May 2001). A total of 7 cases were identified. All available pathologic materials were reviewed, and the histopathologic features were noted. Routine histologic sections were prepared from 10% formalin-fixed, paraffin-embedded tissue, sectioned at 5 μm and stained with H&E. In each case, more than 50% of the tissue removed at the time of surgery was examined histologically.

After review of the H&E-stained material from each case, a representative formalin-fixed, paraffin-embedded tissue block from each case was selected that contained the most chronic inflammatory cells. Then 5-μm sections were

Table 1
Summary of Immunoperoxidase Antibodies Used in the Study

Antibody	Manufacturer	Clone	Antibody Class/ Isotype	Control Tissue	Cell Type Stained	Dilution	Incubation Time (min)
CD3	Novocastra (Burlingame, CA)	Polyclonal	IgG2a	Tonsil	T lymphocyte	1:2	32
CD4	Novocastra	IFC	IgG1	Tonsil	Helper/inducer T-lymphocyte subset	1:10	32
CD5	Novocastra	4C7	IgG1, kappa	Tonsil	T lymphocyte	1:10	15
CD7	Novocastra	272	IgG1	Tonsil	T lymphocyte	1:20	32
CD8	DAKO (Carpinteria, CA)	144B	IgG1, kappa	Tonsil	Cytotoxic/suppressor T-lymphocyte subset	1:20	32
CD10	Novocastra	56C6	IgG1	Tonsil	Germinal center B lymphocytes	1:5	32
CD20	DAKO	L26	IgG2a, kappa	Tonsil	B lymphocytes	1:50	32
CD56	Cell Marque (Hot Springs, AR)	123C3.D5		Neuroblastoma	Natural killer lymphocyte	Undiluted	32
CD68	DAKO	PG-M1	IgG3, kappa	Tonsil	Monocytes and macrophages, microglial cells	1:10	32
CD79a	DAKO	JCB117	IgG1, kappa	Tonsil	Pre-B cells	1:10	32
LMP-1	DAKO	CS1, CS2, CS3, CS4 cocktail	IgG1, kappa	Tonsil	LMP-1 antigen encoded by *BNLF1* gene of Epstein-Barr virus	1:25	32

LMP, latent membrane protein.

cut from each block on charged slides, and the following immunoperoxidase stains were performed on each case: CD3, CD4, CD5, CD7, and CD8 (T lymphocytes); CD10, CD20, and CD79a (B lymphocytes); CD56 (natural killer lymphocytes); CD68 (monocytes and macrophages); and latent membrane protein (LMP)-1 (Epstein-Barr virus) **Table 1**. Immunohistochemical stains were performed as recommended by the manufacturers using an automated staining system (Ventana ES, Ventana, Tucson, AZ) by the avidin-biotin complex (ABC) technique. Briefly, an unstained slide from each case was rehydrated using xylene and graded alcohol baths. Following this, the slides were washed with tap water for approximately 5 minutes, then washed for 3 cycles of 10 minutes' duration each, followed by blocking with normal mouse serum and 3 additional washes of 10 minutes' duration each. Slides were incubated for a set period in a solution of each antibody. See Table 1 for specific incubation times for each antibody. Microwave antigen retrieval followed by a 15-minute EDTA wash was performed for slides treated with CD3, CD4, and CD7 antibodies. Slides treated with CD5, CD8, CD10, CD20, CD56, and CD79a and LMP-1 antibodies were treated with microwave antigen retrieval followed by a 15-minute wash in sodium citrate. The slides were incubated with the manufacturer's secondary antibody and washed 3 times for 10 minutes' duration each. The slides subsequently were treated with a quenching buffer for 10 minutes, followed by 3 washes of 10 minutes' duration each. All slides next were incubated with the ABC reagent, washed 3 times for 10 minutes each, and incubated with 3,3'-diaminobenzidine tetrahydrochloride for 15 minutes. The slides then were washed 3 times for 10 minutes each and counterstained with hematoxylin.

After application of the primary antibody, slides stained with antibodies to CD3, CD4, CD5, CD7, and CD56 were treated with a signal amplification kit (Ventana). These slides were incubated for 8 minutes with rabbit antimouse IgG heavy and light chains, followed by a wash, after which mouse antirabbit IgG was added and incubated for 8 minutes. After washing, the biotinylated secondary antibody was applied as described in the preceding paragraph.

For each case, the medical records were reviewed for information about sex of the patient, age at the time of surgery, duration of seizures before surgery, additional clinical symptoms and signs, location of the lesion, surgery performed, and follow-up.

Results

Clinical Findings

The clinical features are summarized in **Table 2**. Seven patients, including 4 boys and 3 girls, constituted the study group. At the time of surgery, the patients ranged in age from 4 to 15 years (median, 12 years). All patients had medically intractable seizures at initial examination, ranging in duration from 6 months to 7 years before surgery (mean, 3.5 years). With disease progression, all but 1 patient developed hemiparesis, localized to the affected hemisphere. In addition, 2 patients developed nystagmus, and 1 patient left-sided homonymous hemianopia. One patient had a history of febrile seizures (case 1). One patient (case 7) had a history of concomitant celiac disease.

The affected area was localized radiographically and by electroencephalographic studies to the left hemisphere in 4 patients and the right hemisphere in 3 patients. One patient

Table 2
Summary of Clinical Features of Patients With Rasmussen Encephalitis

Case No./ Sex/Age at Surgery (y)	Duration of Seizures (y)	Additional Symptoms	Laterality	Surgery	Follow-up
1/F/4	1	Right-sided hemiparesis	Left	Left-sided functional hemispherectomy	5 y, no seizures with medication
2/F/12	1	Right-sided hemiparesis	Left	Left-sided functional hemispherectomy	6 mo, no seizures with medication
3/F/15	7	Left-sided hemiparesis, left-sided homonymous hemianopia, nystagmus	Right	Right-sided functional hemispherectomy with excision of amygdala, hippocampus	6 mo, no seizures with medication
4/M/15	3.5	Left-sided hemiparesis	Right	Right-sided functional hemispherectomy	Lost to follow-up
5/M/3.5	0.5	None	Right	Right-sided functional hemispherectomy	2 mo, no seizures with medication
6/M/6	4	Right-sided hemiparesis	Left	Left-sided functional hemispherectomy	7 y, decreased seizures with medication
7/M/15	7	Right-sided hemiparesis, nystagmus	Left	Left-sided functional hemispherectomy	Recent case

was known to have had preoperative implanted grid electrodes. All patients eventually underwent a functional hemispherectomy procedure involving the diseased hemisphere. In addition, the ipsilateral amygdala and hippocampus were removed in 1 patient.

Postoperative follow-up information was available for 5 patients. Four patients had no evidence of seizures while taking antiepileptic medication 2 months, 6 months, 6 months, and 5 years after surgery. One patient had a decrease in seizure frequency 7 years after surgery while taking antiepileptic medication. One patient was lost to follow-up in another country. One case was recent.

Histologic Findings

Histologically, all 7 cases were characterized by focal, leptomeningeal, chronic inflammation, consisting primarily of lymphocytic cells **Image 1**). Foci of parenchymal perivascular chronic inflammation involving both gray and white matter were observed in all cases **Image 2**. Again, the predominant inflammatory cell infiltrate was lymphoid. Smaller numbers of lymphocytes were observed infiltrating into the adjacent parenchyma. All 7 cases were also at least focally marked by the presence of a diffuse microglial cell proliferation and a reactive astrocytosis. Four cases demonstrated discrete microglial nodule formations that were noted exclusively in the gray matter **Image 3**. Focal cortical atrophy also was evident in 5 cases and was marked by a loss of neuronal cells, prominent gliosis, and, in 3 cases, focal spongiform degenerative changes **Image 4**. There was no evidence of vasculitis or granulomas. Rare macrophages or gitter cells were identified focally in 2 cases within the leptomeninges. Viral inclusions were not identified. Cortical

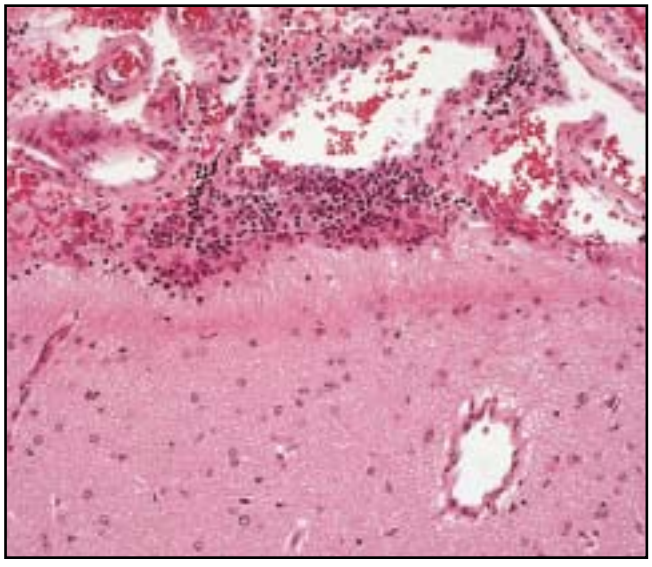

Image 1 (Case 7) Focal, leptomeningeal, chronic inflammation and subpial gliosis (H&E, original magnification ×200).

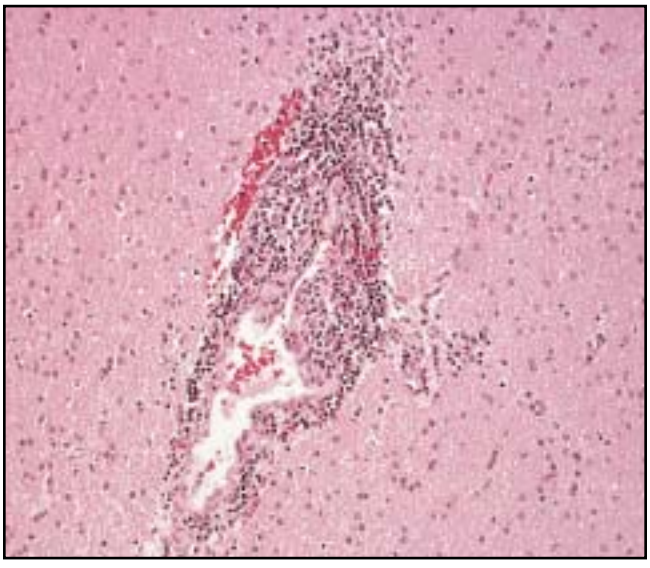

Image 2 (Case 7) A focus of perivascular chronic inflammation involving a white matter vessel (H&E, original magnification ×200).

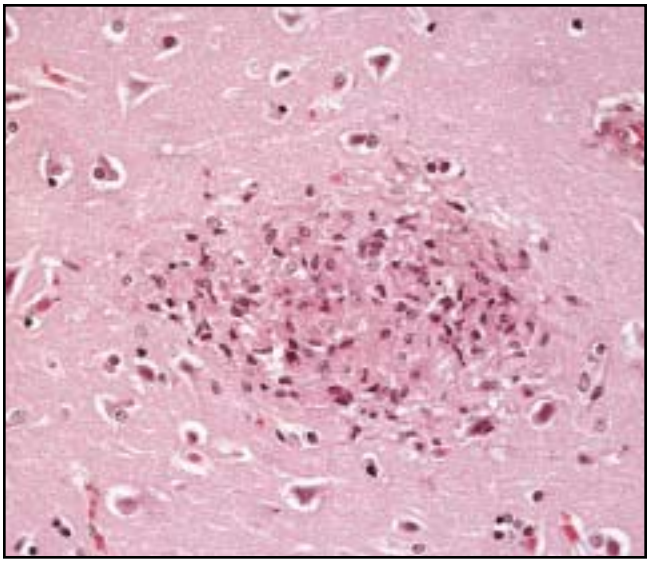

Image 3 (Case 1) An intracortical microglial nodule (H&E, original magnification ×500).

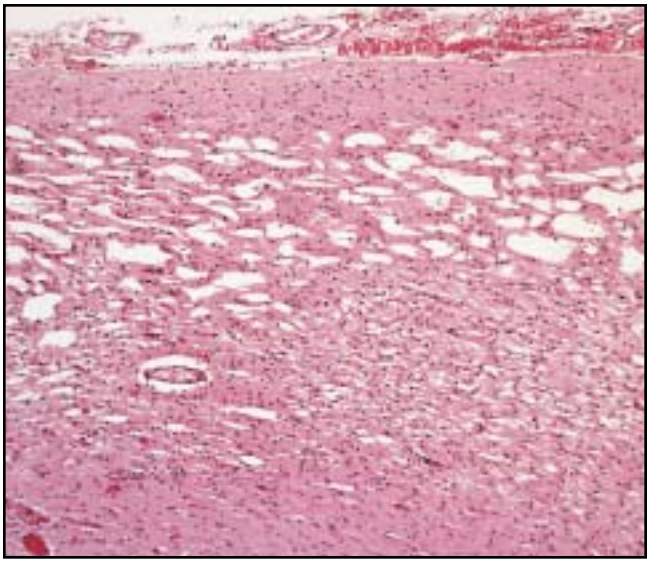

Image 4 (Case 4) Prominent spongiform degeneration marks an area of cortical atrophy (H&E, original magnification ×100).

dysplasia was not observed. There was no evidence of hippocampal sclerosis in the patient who underwent hippocampal resection. There was no evidence of microcalcification. Rare evidence of neuronophagia was noted in 1 case. Of note, the histopathologic findings were present variably in the resected tissue, with a spectrum of disease severity observed in different regions of the excised tissue. In 4 cases, areas that appeared histologically unremarkable were identified.

In 1 case, a concomitant infarct was noted, likely related to a previous surgical excision. Focal areas of subpial gliosis were present in 3 cases. Prominent perivascular white matter atrophy was noted in 2 cases.

Immunohistochemical Results

The immunohistochemical results for each case are summarized in **Table 3**. As evidenced by the prominent CD3 and CD7 immunoreactivity, the vast majority of lymphoid cells observed in all cases, both in the leptomeninges and parenchyma, had a T-cell immunophenotype **Image 5**. Rare B lymphocytes were observed on CD79a immunostaining in all cases; rare CD20+ B lymphocytes were noted in 5 of 7 cases. A subpopulation of cells stained positively with CD5, another T-cell lymphoid marker. The majority of lymphoid cells appeared to have a T-cytotoxic/suppressor immunophenotype and were CD8+ **Image 6**. Rare CD4+ T-helper/inducer lymphocytes were observed in 5 cases. In 1 case, equal numbers of CD4+ and CD8+ lymphoid cells were noted. In another case, no CD4 immunoreactivity was noted. In most cases, only rare CD10+ follicular center B cells were noted on immunostained sections.

Immunoreactivity with CD56, which marks natural killer cells, was not observed in any of the cases. CD68 immunoreactivity was observed in all cases. The cells that marked with the CD68 antibody appeared to have a

Table 3
Summary of Immunohistochemical Staining in Rasmussen Encephalitis*

Case No.	CD3	CD4	CD5	CD7	CD8	CD10	CD20	CD56	CD68	CD79a	LMP-1 (EBV)
1	3+	1+	1+	2+	2+	0	0	0	1+	1+	0
2	3+	0	2+	3+	1+	1+	1+	0	1+	1+	0
3	3+	1+	3+	2+	2+	2+	1+	0	3+	1+	0
4	3+	1+	1+	3+	2+	1+	1+	0	3+	1+	0
5	3+	1+	1+	3+	1+	1+	1+	0	3+	1+	0
6	3+	1+	1+	2+	1+	1+	0	0	1+	1+	0
7	3+	2+	2+	3+	2+	1+	1+	0	3+	1+	0

EBV, Epstein-Barr virus; LMP, latent membrane protein.
* Staining results recorded as absent (0) and graded from 1+ (few) to 3+ (many) to reflect the variable degrees of positivity observed.

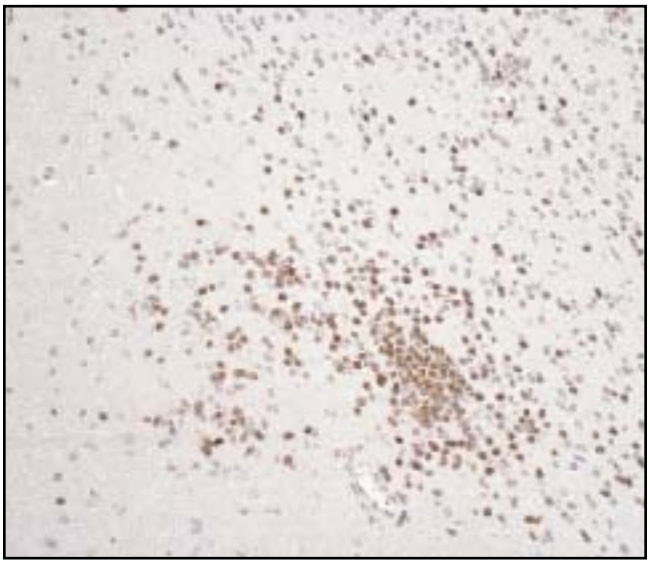

Image 5 (Case 4) The majority of perivascular and parenchymal lymphocytes had a T-cell immunophenotype (CD3+) (original magnification ×400).

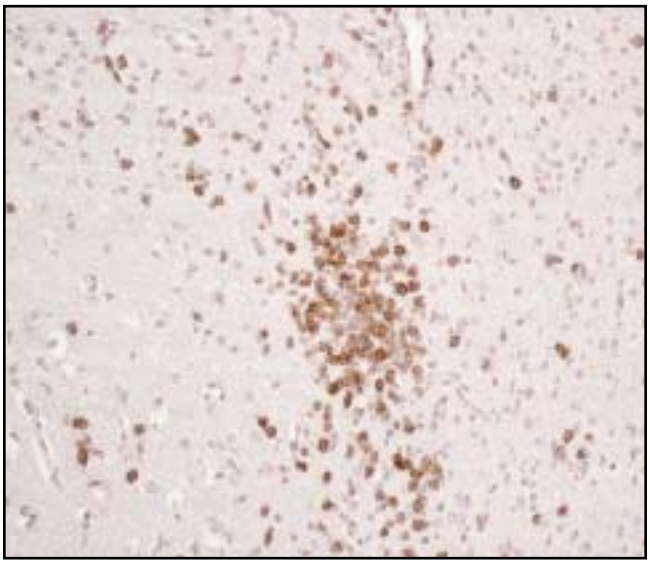

Image 6 (Case 4) The majority of the T lymphocytes in most cases had a T-cytotoxic/suppressor phenotype (CD8+) (original magnification ×400).

microglial cell phenotype and were present in prominent numbers in 4 cases, particularly in microglial nodules. No positivity was observed on immunostaining with LMP-1 antibody, a marker for Epstein-Barr virus. For 3 patients, previous immunohistochemical studies, in situ hybridization, or polymerase chain reaction had been done looking for evidence of cytomegalovirus or herpes simplex virus. In each of these cases, the results were reported as negative.

Discussion

The diagnosis of Rasmussen encephalitis often rests on a combination of characteristic clinical and radiographic findings correlated with tissue pathologic features resembling chronic encephalitis. The typical clinical picture includes a history of intractable epilepsy, usually manifesting during childhood.[1-7] Most patients are pediatric, with manifestation during the first decade of life being most common. Rare examples of similar manifestations in adults, though, have been documented.[8,9] Seizures often are unilateral and tend to spread to involve other areas of the affected side. The disease invariably progresses to neurologic deterioration, resulting in hemiparesis or hemiplegia, homonymous hemianopia, and mental retardation. The rate of deterioration is variable and may range anywhere from months to years. With progression, imaging studies typically demonstrate evidence of unilateral atrophy.[7,10]

The histopathologic picture of Rasmussen encephalitis is quite similar to that of a viral encephalitis and, as in the present cases, is marked by perivascular and leptomeningeal chronic inflammation, gliosis, microglial cell proliferation, and focal cortical atrophy. Relatively few studies have examined, in any detail, the nature of the lymphoid infiltrate. In 1995, Farrell et al[11] reported 7 cases of Rasmussen encephalitis, noting that the majority of lymphoid cells were of T-cell origin, as demonstrated by UCHL-1 positivity. The present study demonstrated similar findings, with the majority of lymphoid cells staining positively with markers of T-cell differentiation (CD3, CD5, and CD7). There was a notable paucity of B-lymphoid cells as evidenced by the relative rarity of positive staining cells with antibodies to CD79a and CD20. Farrell et al,[11] likewise, noted a scarcity of L26+ B lymphocytes. Both studies also recognized an infiltration of predominantly T cells away from the perivascular zone into the adjacent parenchyma.

The present study further detailed the nature of the lymphoid population. The majority of the lymphoid cells seem to have a T-cytotoxic/suppressor immunophenotype, as evidenced by CD8 immunoreactivity. With the exception of 1 case, only rare CD4+ lymphoid cells were identified, and in 1 case, no CD4 immunoreactivity was observed. Because most of the lymphoid cells seem to have a CD8+ immunophenotype and a minimal B-cell response, the inflammatory process seems to be more cellular than humoral. Pardo et al[12,13] noted similar findings and demonstrated the presence of cytokines in tissue that may have a significant role in the neuronal cell injury in this process.

The marker of natural killer cell differentiation (CD56) was negative, and, with the exception of 1 case, only rare

CD10+ follicular center B cells were observed. Similar to the findings of Farrell et al,[11] macrophage markers demonstrated evidence of increased microglial cells. Unfortunately, the specificity of a predominantly T-cell infiltrate in the central nervous system is relatively low in that most inflammatory, including immune, and infectious processes contain relatively large numbers of T cell lymphocytes.[14-16] Even certain neoplastic processes, notably lymphoproliferative disorders, may be marked by large numbers of tumor-infiltrating T lymphocytes. The extent of gliosis and cortical atrophy that marks Rasmussen encephalitis presumably is related to neural cell loss.

The histologic resemblance of the pathologic features in Rasmussen encephalitis to those of viral encephalitis has prompted a search in that direction for a causative agent. Much of the work has focused on the herpesviruses as potential causative agents. Results in this area seem to conflict. Riikonen[17] in 1978 suggested that cytomegalovirus (CMV) may have a role. In 1990, Power et al[18] demonstrated, using in situ hybridization, evidence of CMV genomic material in 7 of 10 patients with Rasmussen encephalitis compared with 2 of 46 control patients. They noted evidence of CMV DNA in neurons, astrocytes, oligodendrocytes, and endothelial cells. Farrell et al[19] failed to subsequently substantiate these findings in a similar in situ hybridization study of 3 patients with Rasmussen encephalitis.

More recently, Vinters et al[20] noted low levels of both CMV and Epstein-Barr virus gene expression in tissue excised from patients with Rasmussen encephalitis; however, they noticed low levels of both viruses in control brain tissues obtained from patients with chronic epilepsy and nonencephalitic lesions. Others have demonstrated evidence of Epstein-Barr virus by in situ hybridization in small numbers of patients.[21] In contrast, Atkins et al[22] were unable to identify evidence of cytomegalovirus, Epstein-Barr virus, and herpes simplex virus using in situ hybridization in 10 cases of Rasmussen encephalitis. Jay et al[23] reported evidence of cytomegalovirus by in situ hybridization in 6 of 10 patients with Rasmussen encephalitis and evidence of herpes simplex virus type 1 in 2 of 10 patients. In the present study, we were unable to demonstrate evidence of Epstein-Barr virus infection by immunohistochemical analysis using LMP-1 antibody in any of the cases. Evaluations by others have also failed to demonstrate evidence of CMV or herpesvirus in the cases examined. Whether the sporadic evidence of viral infection in a subset of patients is of etiologic significance or merely a coincidence is yet to be resolved. The ubiquitous nature of these viruses in the normal population in this age group raises questions about the significance of positive findings.

An immunologic basis to the disorder also has been proposed. Andrews et al[24] in 1990 reported a case of Rasmussen encephalitis associated with a presently elevated antinuclear antibody, cerebrospinal fluid positive for oligoclonal bands, and evidence on resected tissue of granular accumulation of IgG, IgM, IgA, C3, and C1q in blood vessels. They were unable to demonstrate evidence of CMV or herpesvirus 1 antigen on immunostaining. Rogers et al[25] in 1994 reported autoantibodies of glutamate receptor GluR3 in 3 of 4 patients with Rasmussen encephalitis. One patient received plasma exchanges, resulting in a transient reduction in the serum titers of GluR3 antibodies, a decrease in seizure frequency, and an improvement in neurologic function. Ultimately, subsequent evaluation of 4 patients with Rasmussen encephalitis with plasmapheresis demonstrated variable improvement with this treatment modality.[26] Andrews et al[24] hypothesized that focal disruption of the blood-brain barrier in Rasmussen encephalitis permits the focal entry of circulating pathogenic antibodies into the brain that cause focal neural injury and, subsequently, epilepsy. The epilepsy, in turn, results in focal, transient blood-brain barrier disruption that further promulgates this process. Whether an antecedent viral infection somehow triggers the immune response is unknown.

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