Rasmussen encephalitis: Predisposing factors and their potential role in unilaterality

Susanne Fauser1 | Christian E. Elger2 | Friedrich Woermann1,3 | Christian G. Bien1

1Department of Epileptology (Mara Hospital), Medical School, Bielefeld University, Bielefeld, Germany
2Department of Epileptology, University Hospital Bonn, Bonn, Germany
3Society of Epilepsy Research, Bielefeld, Germany

Correspondence
Christian G. Bien, Department of Epileptology (Krankenhaus Mara), Bielefeld University, Campus Bielefeld-Bethel, Maraweg 17-21, 33617 Bielefeld, Germany.
Email: christian.bien@mara.de

Abstract
Objective: Rasmussen encephalitis (RE) is a progressive and destructive inflammatory disease of one hemisphere. Its cause is unknown. We investigated comorbidity and laterality factors that might predispose to RE.

Methods: We retrospectively compared the histories of 160 RE patients to those with genetic generalized epilepsy (n = 154) and those with focal cortical dysplasia Type II (FCD II; n = 148).

Results: The median/mean age at symptom onset in RE was 7/10 years (range = 1–53 years), and 58.1% of the patients were female. The female sex predominated in RE patients, with age > 7 years at disease manifestation. The left hemisphere was affected in 65.6%. Perinatal complications (preterm birth, twin pregnancies, early acquired brain lesions) were more frequent in RE than in control patients. Ipsilateral facial autoimmune conditions (scleroderma en coup de sabre, uveitis, or chorioretinitis) were only observed in RE patients (6.9%). Onset of RE was more frequently associated with fever than that of FCD II. In 33.1% of RE patients, ≥1 potential risk factor was found. Interestingly, 11.9% of patients had one-sided early brain lesions or facial autoimmune lesions ipsilateral to subsequent RE; none had such a lesion contralaterally.

Significance: Perinatal complications and facial autoimmune conditions may act as predisposing factors for RE. Fever might trigger RE manifestation. Further genetic or infectious contributors may be identified in the future. Single or combined hits may be required to elicit or facilitate the start of the disease. Ipsilateral early comorbid lesions or facial autoimmune processes might in part explain the enigmatic unilaterality of RE.

Keywords
autoimmune diathesis, fever association, perinatal problems, Rasmussen encephalitis
1 | INTRODUCTION

Rasmussen encephalitis (RE) is a progressive destructive disease of one cerebral hemisphere, characterized by drug-resistant focal epilepsy, progressive hemiplegia, and cognitive decline, as well as unihemispheric brain atrophy.\(^1\) This disorder is rare and mostly affects children. The peak of disease manifestation has been said to be 6 years of age.\(^2\) The term “encephalitis” indicates that immune cells infiltrate the brains of patients with active disease. Neuropathological studies of brain tissue obtained during surgery for intractable epilepsy have consistently revealed microglial activation and infiltration of round cells. These were later identified to be cytotoxic T cells directed toward neurons and astrocytes.\(^{1,3–6}\) Neuroimaging studies show the sequence from magnetic resonance imaging (MRI) volume and T2/fluid-attenuated inversion recovery signal increase to atrophy and, on positron emission tomography, from hypermetabolism to hypometabolism. Such a course is typical for destructive brain inflammation.\(^{7–9}\) In many cases, the cerebrospinal fluid harbors cells above the normal limit, oligoclonal bands, and increased CD4+ T-cell numbers as well as elevated concentrations of tumor necrosis factor α and granzyme B.\(^{10–12}\) The cause of the chronic encephalitis remains unknown. A unilateral virus infection and genetic factors have been suggested as key elements in this unihemispheric disease.\(^2\)

Authorities in the field have repeatedly stated that RE manifests itself in previously normal children.\(^{13–15}\) None of the three cases of the original description had any abnormalities prior to manifestation of the disease.\(^1\) However, in the large Montreal series (\(N = 48\)), nine patients had perinatal complications (19%), suggesting a higher burden of early problems than often assumed.\(^{16}\)

The etiologies of brain diseases and epilepsies are often multifactorial. Genetic and environmental factors might put an individual at an increased risk of developing an inflammatory brain disease. We hypothesized that this might be the case in RE.

Here, we present a large group of 160 RE cases with demographic data and detailed information on their early history. This large number of patients offers the possibility to detect potential predisposing factors in RE patients beyond those found in other epilepsies. Therefore, we compare the RE cases to 154 patients with genetic generalized epilepsy (GGE) and 148 patients with focal cortical dysplasia (FCD) Type II.

Key Points
- Median/mean age at onset in RE was 7/10 years
- Females predominate beyond age 7 years at manifestation
- Perinatal complications are more common in RE than in genetic generalized epilepsy or focal cortical dysplasia Type II
- Fever-associated disease onset is more frequent in RE than in FCD; 6.9% of RE patients had facial autoimmune conditions
- One or more of these potential risk factors occurred in 33.1% of RE patients; we suggest a multihit etiopathogenesis of RE

2 | MATERIALS AND METHODS

2.1 | Patients with RE

We retrospectively analyzed data of 244 patients with RE. Data of 160 patients were sufficiently detailed to be used for this study. Only cases and controls with data available on age at disease onset, sex, affected hemisphere, pre- and perinatal history, concomitant disease, and MRI findings were included in the study. These were patients of the Epilepsy Center Bethel, Bielefeld, Germany (\(n = 63\)), the Department of Epileptology of the University of Bonn, Germany (\(n = 27\)), or both centers (\(n = 30\)), investigated between 1991 and 2020. They were born between 1948 and 2017, mean 1996, median 1999. For the remaining cases, medical reports or file notes were sent to one of the authors (C.G.B.) to confirm the diagnosis or to obtain advice for patients’ management (\(n = 40\)). In all cases, RE was diagnosed according to the current European consensus criteria\(^\text{17}\) including Olson’s addition (two Part A criteria plus criterion B3, i.e., a positive histopathology).\(^\text{18}\) The series includes surgical and nonsurgical cases; 41 patients underwent hemispherotomy, and a further nine patients lesionectomy, partial resections, or disconnections; the remaining 110 patients were not operated on.

2.2 | Patients with GGE

We retrospectively analyzed the data of 154 patients with GGE. All patients with a diagnosis of GGE who were admitted to the Epilepsy Center Bethel, Bielefeld, Germany, between January 2018 and April 2020 were included. They
were born between 1996 and 2012, mean 2002, median 2001. Patients born later than 2012 mainly did not fulfill the inclusion criteria. Often, they had Dravet syndrome or genetic syndromes accompanied by brain malformation, or their etiologies have not yet been clarified. Therefore, they were not considered for this study. Syndromic diagnoses were taken from the final medical reports: childhood absence epilepsy \((n = 25)\), juvenile absence epilepsy (JAЕ; \(n = 23\)), absence epilepsy not further specified \((n = 6)\), juvenile myoclonic epilepsy (JME; \(n = 33\)), genetic generalized epilepsy with generalized seizures alone \((n = 16)\), genetic generalized epilepsy with grand mal on awakening \((n = 2)\), epilepsy with eyelid myoclonia/Jeavons syndrome \((n = 7)\), generalized epilepsy with febrile seizures plus (GEFS+; \(n = 6\)), myoclonic epilepsy of infancy \((n = 1)\), myoclonic astatic epilepsy \((n = 3)\), and GGE not further specified \((n = 32)\).

### 2.3 Patients with FCD

We retrospectively analyzed data of 148 patients with FCD Type II. All patients who underwent presurgical assessment at the Epilepsy Center Bethel, Bielefeld, Germany, between January 2017 and December 2020 with a final diagnosis of FCD Type II and sufficiently detailed information were included. Patients were born between 1959 and 2018, mean 1996, median 1998. The diagnosis of FCD Type II was histologically confirmed after epilepsy surgery \((n = 114)\) or diagnosed by MRI criteria \((n = 34)\); blurred gray–white matter transition, cortical thickening, and transmantle sign, i.e., FCD IIB).

### 2.4 Analyzed parameters

S.F. extracted all data from the patients’ medical reports and file notes, which were accessible in full to all authors from Mara Hospital. In a descriptive manner, we characterized the three groups regarding these demographic and laterality parameters:

- **Age at disease onset.** “Onset” was defined as the point in time that the treating clinicians considered the best approximation of the first signs of the disease; in the GGE and FCD patients, it was the date of the first seizure. Age is given in years as whole numbers (first year of life = 1, second year of life = 2, and so on).
- **Sex.**
- **Affected hemisphere.** In the RE cases, this was the one with dominant atrophy, producing the dominant lateralizing semiological elements and the dominant abnormal electroencephalographic features. No patient was diagnosed as having bilateral disease. Single cases did not become seizure-free despite anatomical or complete functional hemispherectomy (according to postoperative MRI). In these cases, it remains open whether they had bilateral (even though asymmetrical) RE or whether they had developed a secondary independent epileptic focus in the contralateral hemisphere. In the FCD cases, this was the hemisphere harboring the lesion. In the GGE patients, no affected hemisphere was noted.

As potential risk factors, we studied the following parameters:

- **Acquired factors:**
  - At least one of the following pre- or perinatal problems:
    - Twin pregnancy
    - Premature birth (≤36 weeks)
    - Comorbid early acquired intracerebral lesions, documented by MRI and not specifically related to RE
  - Fever-associated disease onset (maximal latency 1 month). This was not evaluated in the GGE group because it could not be clearly separated in these conditions (e.g., in GEFS+).
  - Febrile seizures (febrile convulsions years before the epilepsy started).
- **Genetic factors**
  - Autoimmune diathesis: history of autoimmune diseases and allergies as documented in the medical records

### 2.5 Statistical analyses, ethics

Pearson chi-squared test was used to compare the potential risk factors between patients with RE, GGE, and FCD (IBM SPSS Statistics Subscription 11–2018). To account for six tests, the significance level of \(p < .05\) was corrected to \(p < .008\) according to Bonferroni.

For this retrospective report of patients studied personally by the authors, informed consent from the patients or their representatives was waived by the ethics committee in Münster (MS 2017-431-f-S) in accordance with the Health Data Protection Law of the Federal State of North Rhine Westphalia.

### 3 RESULTS

#### 3.1 Age at onset, sex distribution, affected hemispheres

Age at symptom onset ranged from 1 to 53 years, median 7 years, mean 10 years. The patients were younger
than those with GGE and older than those with FCD at disease manifestation (Table 1, Figure 1). Females were more frequently affected in both RE and GGE (58.1% and 55.8%, respectively). In FCD patients, there were slightly more males (52.0%). The sex distribution in RE was not the same across all age groups. In patients with onset before the age of 7 years, it was balanced. In patients with later onset (>7 years), females predominated (female:male = 54:25 = 2.2:1). A similar age-related sex distribution was seen in our GGE group. The female sex predominated in patients with seizure onset between 10 to 17 years (female:male = 56:34 = 1.6:1). In this age group, the syndromes JME and JAE were common. In FCD patients, sex distribution was not age related (Figure 1). In the RE group, the left hemisphere was more often affected (65.6%) than in FCD patients (46.6%).

### 3.2 Potential risk factors

Detailed data are given in Table 2.

#### 3.2.1 Early pre- or perinatal problems

Early pre- or perinatal problems were significantly more frequent in RE than in GGE or FCD patients. More specifically, twin pregnancies were reported in 12 RE patients (7.5%), whereas there were no twins in the FCD group and only three (1.9%) in the GGE group. Early comorbid structural lesions were seen on MRI in 12 (7.5%) RE patients, which was more common than in GGE (n = 1, 0.6%) or FCD (n = 3, 2.0%). The etiology of comorbid lesions in RE patients was as follows: ipsilateral peri- or intraventricular pre-/peripartal bleeding (n = 3), ipsilateral small paraventricular infarction (n = 2), ipsilateral enlarged lateral ventricle with peripartal hypoxia (n = 2), ipsilateral cerebellar cortical defects (n = 2), bilateral periventricular leukoencephalopathy (n = 2), and sagittal craniosynostosis (n = 1). Figure 2 depicts examples of patients with early comorbid lesions. Sometimes, the clinical history supported the presence of the lesion very early in life, years before RE manifestation. An example is given in the legend to Figure 2C,D, Patient 23. Interestingly, in nine patients with lateralized lesions, all the lesions were in the same hemisphere as the encephalitis (the other three lesions were bilateral).
TABLE 2  Potential predisposing factors in RE patients compared to GGE and FCD patients

| Factor                                | RE, n = 160 | GGE, n = 154 | FCD, n = 148 |
|---------------------------------------|-------------|--------------|--------------|
| Acquired factors                      |             |              |              |
| Early pre- or perinatal problems      | 26 (16.3%)  | 5 (3.2%)     | 4 (2.7%)     |
| Fever-associated disease manifestation| 24 (15.0%)  |              | 0            |
| Febrile seizure                       | 5 (3.1%)    | 21 (13.6%)   | 5 (3.4%)     |
| Genetic factors                        |             |              |              |
| Autoimmune diathesis                  | 39 (24.4%)  | 37 (24.0%)   | 26 (17.6%)   |

Abbrevations: FCD, focal cortical dysplasia; GGE, genetic generalized epilepsy; RE, Rasmussen encephalitis.

^Significant after Bonferroni correction (p < .008).

See Materials and Methods section for explanation.

FIGURE 2  Examples of early comorbid lesions. Patient 64: This male patient has suffered from left-hemispheric Rasmussen encephalitis (RE) since he was 6 years old. (A) First magnetic resonance imaging (MRI) was performed 1 month after epilepsy (i.e., RE) manifestation. It showed an old left cerebellar gliotic defect (large arrow) and a small hyperintense lesion in the left posterior putamen (small arrow). (B) Three years later, there was a distinct atrophy with increased T2 signal of the left striatum (small arrows) and the left pallium. The gliotic cerebellar lesion (large arrow) was unchanged during the complete follow-up. Patient 23: After a complicated pregnancy, this female patient was born at term. At the age of 8 weeks, pyramidal tract signs with right-sided pathologically increased muscle reflexes became evident. Moreover, language development was delayed from the beginning. (C) An MRI was performed at the age of 4 years with epilepsy onset (i.e., left-sided RE) and already showed a shrunken putamen on the left side, predominantly in the posterior part (large arrow); the claustrum was no longer discernable (small arrow). In the following years, she developed a progressive right-sided hemiparesis. (D) At the age of 14 years, MRI showed a loss of the striatum (caudate nucleus and putamen) and a perisylvian atrophy (small arrows) on the left. Moreover, left-hemispheric atrophy (large arrows) was seen.
3.2.2 | Fever-associated disease onset

Fever-associated disease manifestation was significantly more common in RE than in FCD patients. In RE patients, we observed a decreasing frequency of febrile onset with increasing age at onset (ages 1–6 years: febrile onset in 15/68 [22%]; ages 7–15: febrile onset in 8/70 [11%]; ages 16–53: febrile onset in 1/22 [5%]).

3.2.3 | Febrile seizures

In the RE patients, febrile seizures (years before disease manifestation) were reported in only five patients (3.1%). There was no significant difference compared with FCD patients. The proportion of 3% lies within the 2%–5% range of the incidence of febrile seizures in the Western world. By contrast, significantly more GGE patients (21/154, 13.6%) had febrile seizures.

3.2.4 | Autoimmune diathesis

Overall, there was no significant difference in the frequency of autoimmune diseases or allergies in general between the different groups. However, scleroderma en coup de sabre (n = 9), uveitis (n = 1), and chorioretinitis (n = 1) were seen exclusively in 11 RE patients (6.8%). These lateralized conditions occurred ipsilaterally to the hemisphere affected by RE in all cases. They always preceded the cerebral manifestation. Patients with scleroderma en coup de sabre often had additional ipsilateral facial atrophy (Parry–Romberg syndrome). The scleroderma patients were characterized by a late onset of cerebral symptoms (between 7 and 12 years).

Figure 3 shows a patient with scleroderma en coup de sabre, ipsilateral T-cell-dominated encephalitis, and progressive cerebral hemiatrophy.

3.3 | Combinations of potential predisposing factors

Perinatal complications, facial autoimmunity, and a fever-associated disease onset occurred isolated in 42 and in combination in 11 patients. Altogether, there were 53 of 160 RE patients with potential predisposing factors (33.1%). Table 3 summarizes the patients with comorbidity factors.

4 | DISCUSSION

This study presents the largest group of patients with RE in the literature. It provides basic data on demographics and laterality as well as on potential predisposing factors. Whereas most larger series are surgical cohorts, the present series covers surgical and nonsurgical cases and therefore gives a more complete picture.

4.1 | Demographic data

The median/mean age at onset in our series (7/10 years) was higher than in previous smaller series that gave medians between 5 and 6.1 years and means between 4 and 7.2 years. This difference may be related to the aforementioned series often being surgical series. Hemispherectomy/hemispheric deafferentation is performed more frequently in younger patients.

In the present series, females predominated (58.1%). Previous series reported an equal sex distribution: 114 of 228 pooled patients in eight nonoverlapping series with >15 patients were female (50.0%). This may be related to their younger age at onset; in the present series, too, the younger patients had an equal sex distribution. A review of late onset RE, by contrast, showed a 4:1 female preponderance. Our patient group comprised patients with a wide range of age at disease manifestation (1–53 years), which may explain the female preponderance.

In our cohort, the left hemisphere was more frequently affected than the right one (65.6%). Five previous series that gave lateralization data suggested a higher frequency of right-hemispheric RE (pooled data: 101/185, 54.6%). This may be related to these being predominantly surgical series; right-hemispheric operations are more readily performed than left-sided procedures. In all patients, unilateral RE was observed. It would be interesting to investigate in long-term follow-up why few cases did not become seizure-free and whether single cases also develop contralateral affection.

4.2 | Acquired factors

Our RE patients more frequently had early (pre- and perinatally) acquired structural lesions, perinatal complications, or fever-associated disease onset compared to the controls.

Similar to our observations, the Montreal group described perinatal complications in 19% of RE patients. These lesions could act as promotive factors in a “multiple hit” cascade.

Another promotive comorbidity factor in a multiple hit model may be a febrile viral infection. In line with this theory, we found frequent (15.0%) cases with febrile (probably viral) infections preceding RE manifestation. Fever-associated disease onset was documented in 38% of RE
patients of the Montreal series. As in the present study, the febrile illnesses occurred within 1 month before disease onset and were usually nonspecific, probably viral upper respiratory infections. Molecular mimicry, bystander activation, or viral persistence have been suggested in several autoimmune diseases. Moreover, a virus-induced leukopenia was discussed, followed by a peripheral T-cell renewal leading to a drift in T-cell receptors toward greater self-reactivity. Febrile onset was more common in younger patients. In adult patients, febrile onset seems to no longer play a prominent role.

Our RE patients frequently had twins (7.5%; none of the other twins were affected by RE). For comparison, according to the Hellin–Zeleny law, one expects 1.1%–1.2% of births to be twin births. The actual proportion in Germany in 2015 was 1.8%, which still is much lower than the proportion in RE. In most cases, the twins were not identical. Thus, we hypothesize that an adverse in utero environment may play a role. Twin pregnancies may lead to premature delivery and thus to early structural complications such as intracerebral bleedings or periventricular leukoencephalopathy. In our series, not all twins had structural lesions, but subtle defects cannot be excluded. Also, preterm birth may give rise to immunological particularities.

As the three cohorts were born in similar years, the change of background population twinning rate over the course of time probably does not account for the differences between the groups.

4.3 Genetic risk factors

Ipsilateral uveitis, chorioretinitis, or scleroderma were specifically associated with RE. The co-occurrence of RE with ipsilateral uveitis or Parry–Romberg syndrome has been described earlier. An underlying genetic mosaicism has been considered in the subgroup with Parry–Romberg syndrome, especially in those with additional segmental vitiligo, and may also apply in patients with

FIGURE 3 Example of comorbid facial autoimmune condition. Patient 148: In this male patient, right-hemispheric Rasmussen encephalitis manifested itself at age 22 years. (A) At the age of 10 years, he developed scleroderma en coup de sabre with right-sided lateralization (the scarlike lesion bulges out to the right at the superior end and terminates at the medial aspect of the right eyebrow, arrows). (B) Magnetic resonance imaging (MRI) at the age of 23 years showed a right temporo-occipital lesion. After lesionectomy, histology showed T-lymphocytic infiltrates. (C) The MRI after lesionectomy at the age of 24 years revealed no clear atrophy. (D) At the age of 39 years, right-sided hemiatrophy is discernable.
| Patient ID | Age at onset, years | Scleroderma (S)/uveitis (U)/chorioretinitis (C) | Twins | Premature birth, ≤36 weeks | Structural early brain lesion | Fever-associated disease onset or infection |
|------------|---------------------|-----------------------------------------------|-------|----------------------------|-----------------------------|---------------------------------------|
| 1          | 1                   |                                               |       | +                          |                             | +                                     |
| 3          | 1                   |                                               |       | +                          |                             | +                                     |
| 4          | 2                   |                                               |       | +                          |                             | +                                     |
| 14         | 3                   | + (U)                                         | +     | +                          |                             | +                                     |
| 16         | 3                   |                                               |       | +                          | +                           | +                                     |
| 18         | 3                   |                                               | +     | +                          | +                           | +                                     |
| 19         | 3                   |                                               |       | +                          | +                           | +                                     |
| 20         | 3                   |                                               |       | +                          | +                           | +                                     |
| 21         | 3                   |                                               |       | +                          | +                           | +                                     |
| 23         | 4                   |                                               |       | +                          | +                           | +                                     |
| 27         | 4                   |                                               |       | +                          | +                           | +                                     |
| 32         | 4                   |                                               | +     | +                          | +                           | +                                     |
| 34         | 4                   |                                               |       | +                          | +                           | +                                     |
| 37         | 4                   |                                               |       | +                          | +                           | +                                     |
| 39         | 4                   |                                               |       | +                          | +                           | +                                     |
| 43         | 5                   |                                               |       | +                          | +                           | +                                     |
| 46         | 5                   |                                               |       | +                          | +                           | +                                     |
| 49         | 5                   |                                               |       | +                          | +                           | +                                     |
| 50         | 5                   |                                               |       | +                          | +                           | +                                     |
| 51         | 5                   |                                               |       | +                          | +                           | +                                     |
| 54         | 5                   |                                               |       | +                          | +                           | +                                     |
| 55         | 6                   |                                               |       | +                          | +                           | +                                     |
| 57         | 6                   |                                               |       | +                          | +                           | +                                     |
| 59         | 6                   |                                               |       | +                          | +                           | +                                     |
| 60         | 6                   |                                               |       | +                          | +                           | +                                     |
| 64         | 6                   |                                               |       | +                          | +                           | +                                     |
| 70         | 7                   |                                               |       | +                          | +                           | +                                     |
| 73         | 7                   |                                               | +     | +                          | +                           | +                                     |
| 75         | 7                   | + (S)                                         |       | +                          | +                           | +                                     |
| 82         | 8                   |                                               |       | +                          | +                           | +                                     |

(Continues)
| Patient ID | Age at onset, years | Scleroderma (S)/uveitis (U)/chorioretinitis (C) | Twins | Premature birth, ≤36 weeks | Structural early brain lesion | Fever-associated disease onset or infection |
|------------|---------------------|-----------------------------------------------|--------|--------------------------|-------------------------------|---------------------------------------------|
| 87         | 8                   |                                               |        | +                        |                               |                                             |
| 88         | 8                   |                                               |        | +                        |                               |                                             |
| 89         | 8                   |                                               |        | +                        |                               |                                             |
| 95         | 9                   |                                               |        |                           |                               |                                             |
| 96         | 9                   |                                               |        |                           |                               |                                             |
| 103        | 9                   | + (S)                                         |        |                           |                               |                                             |
| 105        | 9                   |                                               |        |                          |                               |                                             |
| 107        | 9                   |                                               |        |                           |                               |                                             |
| 111        | 10                  |                                               |        |                           |                               |                                             |
| 112        | 10                  | + (S)                                         |        |                          |                               |                                             |
| 116        | 11                  |                                               |        |                          |                               |                                             |
| 117        | 11                  | + (S)                                         |        |                          | +                             |                                             |
| 122        | 11                  | + (S)                                         |        |                          |                               |                                             |
| 123        | 11                  |                                               |        |                          |                               |                                             |
| 128        | 13                  |                                               |        |                          |                               |                                             |
| 131        | 14                  |                                               |        |                          | +                             | +                                           |
| 135        | 14                  | + (S)                                         |        |                          |                               |                                             |
| 136        | 15                  |                                               |        |                          |                               |                                             |
| 141        | 18                  |                                               |        |                          | +                             | +                                           |
| 148        | 22                  | + (S)                                         |        |                          |                               |                                             |
| 149        | 23                  | + (S)                                         |        |                          |                               |                                             |
| 154        | 28                  | + (S)                                         |        |                          |                               |                                             |
| 155        | 30                  | + (C)                                         |        |                          |                               |                                             |
RE and ipsilateral uveitis or chorioretinitis. The preponderance of the female sex is compatible with an autoimmune aspect of RE; other autoimmune conditions, too, are more frequent in females.43 Ipsilateral facial autoimmunity was observed predominantly in older teenagers, giving further hints to the hypothesis that late onset RE may be different from childhood onset RE.

4.4 Laterality of potential predisposing factors and a pathogenetic model of RE

Interestingly, nine patients had unilateral early acquired structural brain lesions in the hemisphere subsequently impacted by encephalitis. No patient had one-sided contralateral lesions. The 11 patients with facial autoimmune diseases also had their skin or eye affected on the side later intracranially affected by RE. In summary, 19 of 160 RE cases (11.9%) had preexisting ipsilateral abnormalities (Patient 117 had both an old ischemic lesion and Parry–Romberg syndrome), which might contribute to the enigmatic unilaterality of RE. We suggest a multihit model for the development of RE, with early lesions, facial autoimmunity, or febrile onset being predisposing factors.

Previously, researchers suggested such a pathogenetic concept comprising several hits when discussing the role of antibodies against the ionotropic glutamate receptor 3 (GluR3 antibodies). They suggested a trauma or an infection as first hits that may disrupt the blood–brain barrier, allowing GluR3 antibodies access. The second element would be the presence of antibodies or the ability to produce them. As a third factor, antigen display on neurons was postulated.44 Although the specificity of GluR3 antibodies for RE could not be confirmed,45 the multiple-hit hypothesis remains interesting and has, in a speculative manner, been taken up by another group.30 These authors presumed that perinatal hypoxia or infection may set off the disease process and may even be responsible for neural migration defects, which have been observed in some RE patients.30

Pre- and perinatal problems may start chronic encephalitis by damaging neurons and releasing neural proteins that act as autoantigens once they reach the regional lymph nodes and are presented to the adaptive immune system. Early complications may also disrupt the blood–brain barrier and permit antibody access to the brain. Any of these events may predispose patients to subsequent (“secondary”) autoimmune encephalitis. Incidental concomitant pathological findings (dysplasia, tumor, tuberous sclerosis, cavernoma) in surgical specimens of RE patients (i.e., ipsilateral samples) have also been observed and tentatively interpreted in the sense of a multistage pathogenesis.46,47

Our observation of a preceding ipsilateral pathology in 11.9% of patients in this large series would be compatible with a lateralizing element within a multihit pathogenesis. In line with this, the “fertile field concept” suggests an interaction of different pathogenic mechanism as a prerequisite for a subsequent immunopathological reaction.29 Regarding RE, a hemispheric mosaic of specific genetic peculiarities or a unihemispheric viral infection have recently been discussed as other potential hemispheric pathogenic elements.2,48

4.5 Combination of comorbid factors

In one fifth of patients with comorbidity factors, more than one of these factors were seen. Such a coincidence of potential risk factors may indicate that, sometimes, several promotive circumstances may be required to exceed the threshold of RE manifestation.

4.6 Factors not specifically associated with RE

Febrile seizures (occurring years before disease manifestation) were as rare in RE patients as in the normal population (2%–5%).19 Hashimoto thyreoiditis, ulcerative colitis, and Crohn disease were very rare in RE patients and no more common than in the control groups. This stands in contrast to the hypothesis raised in an earlier case report, which suggested shared mechanisms of susceptibility between RE and comorbid autoimmune diseases (Hashimoto thyroiditis, ulcerative colitis, Crohn disease, and systemic lupus erythematosus).49 Moreover, autoimmune diseases like bronchial asthma, atopic dermatitis, pollinosis, and diverse allergies were also not particularly frequent in RE patients. Thus, a general, nonspecific autoimmune predisposition is not evident. This observation may be of practical value, as it is reassuring for patients with autoimmune diseases.

4.7 Limitations

This was a retrospective study, with all the inherent weaknesses. The two large comparator groups analyzed in the same manner were included to counterbalance this as much as possible. It cannot be excluded that certain variables are more prone to bias than others, for example, underrecognition of facial autoimmunity in non-RE patients. However, a standardized scheme for collecting patients’ medical history in Bethel including all reported variables minimizes this bias. Patients were
investigated at tertiary epilepsy centers, which may have led to a bias in favor of more severely affected cases; little is known about mildly affected RE cases not seeking help at epilepsy centers.

5 | CONCLUSIONS

RE is more frequent in females and is associated with several potential risk factors in a substantial subset of patients (33.1%). This is compatible with the hypothesis that RE is promoted or triggered by genetic and/or acquired comorbidities. Looking at cases with ipsilateral early brain lesions or ipsilateral facial autoimmune diseases, these hits may in part explain the unilateral nature of RE. An additional hemispheric mosaic or a unihemispheric viral infection has been suggested. In either case, disease manifestation may be facilitated by the potential risk factors discussed here. Moreover, febrile infections may boost the immune system and set off RE.

ACKNOWLEDGMENTS

S.F. was supported by a research grant offered by the Epilepsie-Akademie Berlin-Bethel, which is sponsored by the von Bodelschwingh Foundation Bethel, Bielefeld, Germany. Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

C.G.B. receives research support from Deutsche Forschungsgemeinschaft (German Research Council, Bonn, Germany) and Gerd-Altenhof-Stiftung (Deutsches Stiftungs-Zentrum, Essen, Germany). None of the other authors has any conflict of interest to disclose.

ORCID

Susanne Fauser © https://orcid.org/0000-0003-3063-1586
Christian G. Bien © https://orcid.org/0000-0003-2225-8654

REFERENCES

1. Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. Neurology. 1958;8:435–45.
2. Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol. 2014;13:195–205.
3. Robitaille Y. Neuropathologic aspects of chronic encephalitis. In: Andermann F, editor. Chronic encephalitis and epilepsy: Rasmussen's syndrome. Boston, MA: Butterworth-Heinemann; 1991. p. 79–110.
4. Farrell MA, Droogan O, Secor DL, Poukens V, Quinn B, Vinters HV. Chronic encephalitis associated with epilepsy: immunohistochemical and ultrastructural studies. Acta Neuropathol. 1995;89:313–21.
5. Bien CG, Bauer J, Deckwerth TL, Wiendl H, Deckert M, Wiestler OD, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. Ann Neurol. 2002;51:311–8.
6. Bauer J, Elger CE, Hans VH, Schramm J, Urbach H, Lassmann H, et al. Astrocytes are a specific immunological target in Rasmussen's encephalitis. Ann Neurol. 2007;62:67–80.
7. Bien CG, Urbach H, Deckert M, Schramm J, Wiestler OD, Lassmann H, et al. Diagnosis and staging of Rasmussen's encephalitis by serial MRI and histopathology. Neurology. 2002;58:250–7.
8. Granata T, Gobbi G, Sprefico R, Vigevano F, Cavopilla G, Ragona F, et al. Rasmussen's encephalitis: early characteristics allow diagnosis. Neurology. 2003;60:422–5.
9. Maeda Y, Oguni H, Saitou Y, Mutoh A, Imai K, Osawa M, et al. Rasmussen syndrome: multifocal spread of inflammation suggested from MRI and PET findings. Epilepsia. 2003;44:1118–21.
10. Rasmussen T. Further observations on the syndrome of chronic encephalitis and epilepsy. Appl Neurophysiol. 1978;41:1–12.
11. Rasmussen T, Andermann F. Update on the syndrome of chronic encephalitis and epilepsy. Cleveland Clin J Med. 1989;56(Suppl 2):S181–4.
12. Takahashi Y, Mine J, Kubota Y, Yamazaki E, Fujiwara TA. Substantial number of Rasmussen syndrome patients have increased IgG, CD4+ T cells, TNFalpha, and granulyme B in CSF. Epilepsia. 2009;50:1419–31.
13. Dulac O. Rasmussen's syndrome. Curr Opin Neurol. 1996;9:75–7.
14. Vining EP. Struggling with Rasmussen's syndrome. Epilepsy Curr. 2006;6:20–1.
15. Bulteau C, Grosmaitre C, Save-Pédebos J, Leunen D, Delalande O, Dorfmüller G, et al. Language recovery after left hemispherotomy for Rasmussen encephalitis. Epilepsy Behav. 2015;53:51–7.
16. Oguni H, Andermann F, Rasmussen TB. The syndrome of chronic encephalitis and epilepsy. A study based on the MNI series of 48 cases. Adv Neurol. 1992;57:419–33.
17. Bien CG, Granata T, Andermann F, Oguni H, Rasmussen TB, et al. Diagnosis and staging of Rasmussen encephalitis: a European consensus statement. Brain. 2005;128:454–71.
18. Olson HE, Lechpammer M, Prabhu SP, Ciarlini PD, Poduri A, Gooty VD, et al. Clinical application and evaluation of the Bien diagnostic criteria for Rasmussen encephalitis. Epilepsia. 2013;54:1753–60.
19. Waruiru C, Appleton R. Febrile seizures: an update. Arch Dis Child. 2004;89:751–6.
20. Longaretti F, Dunkley C, Varadkar S, Varga-Khadem F, Boyd SG, Cross JH. Evolution of the EEG in children with Rasmussen's syndrome. Epilepsia. 2012;53:1539–45.
21. Granata T, Maticardi S, Ragona F, Freri E, Casazza M, Villani F, et al. Hemispherotomy in Rasmussen encephalitis: long-term outcome in an Italian series of 16 patients. Epilepsy Res. 2014;108:1106–19.
22. Pardo CA, Vining EP, Guo L, Skolasky RL, Carson BS, Freeman JM. The pathology of Rasmussen syndrome: stages of cortical involvement and neuropathological studies in 45 hemispherectomies. Epilepsia. 2004;45:516–26.
23. Caraballo R, Bartuluchi M, Cersósimo R, Soraru A, Pomata H. Hemispherectomy in pediatric patients with epilepsy: a study...
of 45 cases with special emphasis on epileptic syndromes. Child Nerv Syst. 2011;27:2131–6.
24. Bellamkonda N, Phillips HW, Chen J-S, Tucker AM, Maniquis C, Mattern GW, et al. Epilepsy surgery for Rasmussen encephalitis: the UCLA experience. J Neurosurg Pediatr. 2020;26:389–97.
25. Vining EP, Freeman JM, Pillas DJ, Uematsu S, Carson BS, Brandt J, et al. Why would you remove half a brain? The outcome of 58 children after hemispherectomy—the Johns Hopkins experience: 1968 to 1996. Pediatrics. 1997;100:163–71.
26. Dupont S, Gales A, Sammey S, Vidalheth M, Lambrecq V. Late-onset Rasmussen encephalitis: a literature appraisal. Autoimmun Rev. 2017;16:803–10.
27. Oguni H, Andermann F, Rasmussen TB. The natural history of the syndrome of chronic encephalitis and epilepsy: a study of the MNI series of forty-eight cases. In: Andermann F, editor. Chronic encephalitis and epilepsy: Rasmussen’s syndrome. Boston, MA: Butterworth-Heinemann; 1991. p. 7–35.
28. Pellegrin S, Baldeweg T, Pujar S, D’Arco F, Cantalupo G, Fujinami RS, von Herrath MG, Christen U, Whitton JL. Focal encephalitis and epilepsy: Rasmussen’s syndrome. Neurology. 2001;57:1511–4.
29. Rhodes RH, Lehman RM, Wu BY, Roychowdhury S. Focal chronic inflammatory epileptic encephalopathy in a patient with malformations of cortical development, with a review of the spectrum of chronic inflammatory epileptic encephalopathy. Epilepsia. 2007;48:1184–202.
30. Hellin D. Die Ursache der Multiparität der uniparen Tiere überhaupt und der Zwillingschwangerschaft beim Menschen insbesondere. Munich, Germany: Seitz und Schauer; 1895.
31. Zeleny C. The relative numbers of twins and triplets. Science. 1921;53:262–3.
32. Statistisches Bundesamt Verteilung der Zwillingsgeburten in Deutschland nach Geschlecht der Kinder im Jahr 2015. 2020. https://de.statista.com/statistik/daten/studie/1281/umfrage/anzahl-der-zwillingsgeburten-in-deutschland-2006/. Accessed 22 Dec 2020.
33. Goedicke-Fritz S, Härlt C, Krasteva-Christ G, Kopp MV, Meyer S, Zemlin M. Preterm birth affects the risk of developing immune-mediated diseases. Front Immunol. 2017;8:1266.
34. Melville JM, Moss TJM. The immune consequences of preterm birth. Front Neurosci. 2013;7:79.
35. Harvey AS, Andermann F, Hopkins IJ, Kirkham TH, Berkovic SF. Chronic encephalitis (Rasmussen’s syndrome) and ipsilateral uveitis. Ann Neurol. 1992;32:826–9.
36. Sansevere AJ, Henderson LA, Stredny CM, Prabhu SP, Shah A, Sundel R, et al. Posterior-onset Rasmussen’s encephalitis with ipsilateral cerebellar atrophy and uveitis resistant to rituximab. Epilepsy Behav Rep. 2020;14:100360.
37. How to cite this article: Fauser S, Elger CE, Woermann F, Bien CG. Rasmussen encephalitis: Predisposing factors and their potential role in unilaterality. Epilepsia. 2022;63:108–119. https://doi.org/10.1111/epi.17131