Towards a cure for Rasmussen's encephalitis: research strategies

Deirdre Pinto, January 2010[1]

Abstract

Rasmussen's encephalitis (RE) is a rare inflammatory brain disease that causes intractable focal seizures, and progressive motor, sensory and cognitive deficits. There is evidence for an autoimmune aetiology in which T-cells attack a specific unidentified antigen or set of antigens in patients' brains.

RE typically affects previously normal children aged between two and ten years. An unusual feature of the disease, which sets it apart from other inflammatory diseases of the central nervous system, is that it is usually confined to one cerebral hemisphere. This makes possible the only known 'cure' for the condition—surgical hemispherectomy to remove or disconnect the affected side of the brain. However, recent progress in understanding of the disease, and the emergence of therapies that slow disease progression and help control symptoms, has led some researchers to believe that more targeted and effective medical treatments are potentially within reach.

This paper discusses current issues in the treatment of RE and presents strategies to advance research in three broad areas: understanding the pathophysiology of RE; evaluating the effectiveness of RE treatments; and reviewing the potential use in RE of current and emerging therapies for other autoimmune conditions.

The paper argues that the success of future research will depend on stronger collaboration between researchers and—critically—input from a wider range of specialties, including immunologists, molecular biologists, and geneticists.

In addition to benefiting hundreds of RE children and their families worldwide, further breakthroughs in understanding and treating RE could have important implications for a much larger group of patients with intractable seizures, as parallels between RE and other forms of epilepsy are being increasingly recognised.

Introduction

Rasmussen encephalitis (RE) is a rare but severe inflammatory brain disease that leads to the progressive destruction of one cerebral hemisphere over periods ranging from months to ten years or more. While the rate and pattern of the destructive process are highly variable, the deficits ultimately caused by RE are usually severe: they include hemiparesis, ataxia, intellectual decline, personality and behavioural changes, visual problems (homonymous hemianopia), sensory deficits, and speech problems (dysarthria, dysphasia or aphasia).[2] Except in the very rare cases of bilateral RE, the disease is not usually fatal.

RE typically affects previously normal children aged two to ten years. However, some cases begin in adolescence and adulthood. A small bimodal distribution (median ages 5.3 and 18.9 years) has been reported, and as many as 10 per cent of cases appear in early adulthood.[3] The disease has an estimated incidence of between 1/500,000 and 1/1,000,000.[4] There are no known patterns of inheritance.

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1 The author is the aunt of an eleven year old girl, Freya, who has Rasmussen's encephalitis. Over the past five years she has closely monitored peer reviewed journal articles on RE, as well as web-based information from support groups, media reports, patient/family blogs, and has corresponded via email with researchers in Australia, the United States, England and Germany.

2 Rasmussen T and Andermann F. Update on the syndrome of 'chronic encephalitis' and epilepsy, *Cleveland Clinical Journal of Medicine*, 1989; 56 (2): S181–4.

3 Bien CG, Widman G, Urbach H, Sassen R, Kuczaty S, Wiestler OD, Schramm J, and Elger CE. The natural history of Rasmussen's encephalitis, *Brain*, 2002; 125 (8): 1751–9.

4 The Encephalitis Society, www.encephalitis.info/info, accessed 2 January 2010.

Significant advances have been made in recent years in understanding the probable causes of RE. The evidence strongly suggests an autoimmune process, possibly triggered by a viral infection. However, the precise role played by antibody-mediated mechanisms, T-cell immunity and antigens remains elusive.[5]

Clinical features

The first sign of the disease is usually the development of seizures originating from one hemisphere. These are often partial or secondarily generalized tonic-clonic seizures or status epilepticus. Seizures semiology is variable, but motor seizures are often present. Seizures with somatosensory, autonomic, visual, and limbic features may also occur.[6]

Most patients develop a variety of seizure types as inflammation spreads across the affected hemisphere, with seizures becoming increasingly severe and frequent. Epilepsia partialis continua (EPC) develops in at least 50 per cent of cases and its presence is strongly suggestive of RE.[7] EPC is characterised by recurrent, asynchronous, and persistent myoclonias involving different muscle groups of the face, hand, or leg on one side of the body.

The seizures rapidly become refractory, usually with limited response to anti-epileptic drugs (AEDs). EPC and other forms of focal motor seizures are particularly unresponsive to AEDs. Secondarily generalized motor seizures appear to be easier to control.

Bien and his colleagues[8] distinguish two patterns of disease associated with the age at onset of RE; one with an earlier, more severe, and rapidly progressive course starting during childhood and a second with typically a more protracted and milder course starting during adolescence or adult life.

The Bien study separates the progression of the disease into three stages: an initial rather non-specific 'prodromal stage' with a relatively low seizure frequency and, rarely, mild hemiparesis (median duration 7.1 months; range, 0 months to 8.1 years); an 'acute stage' characterized by frequent seizures and rapid neurological deterioration (median duration eight months; range 4 to 8 months); and a 'residual stage' with permanent and stable neurological deficits and still many seizures, although less frequent than in the acute phase.

However, it is not difficult to find reports of cases that defy the categorizations described above. Clinical progression can happen quickly with devastating results: many younger children, in particular, do not have a 'prodromal stage' and enter the acute phase as the initial clinical disease manifestation. In other cases, progression can happen insidiously with periods of acute seizure exacerbation and periods of relative respite over many years. Some patients decline slowly or rapidly after apparently entering the residual stage. Accounts available on the internet, written by patients' family members, suggest that patients may continue to suffer frequent seizures and ongoing cognitive decline for decades after experiencing the first symptoms of RE.

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5 Hart Y. Rasmussen's encephalitis, *Epileptic Disorders*, 2004; 6: 133–144.
6 Engel J, Pedley T A, Aicardi J, Ditcher MA and Moshe S. Epilepsy: A Comprehensive Texbook, Lippincott Williams & Wilkins, 2007.
7 Carney RF. Rasmussen syndrome: intractable epilepsy and progressive neurological deterioration from a unilateral central nervous system disease, *CNS Spectrums*, 2001; 6(5): 398-416.
8 Bien CG,Widman G, Urbach H, Sassen R, Kuczaty S,Wiestler OD, et al. The natural history of Rasmussen's encephalitis, *Brain*, 2002; 125: 1751–9.

Atypical cases

The literature reports a number of pathologically confirmed RE cases with atypical or unusual clinical features.[9] These include early-onset RE (before two years of age), bilateral cerebral involvement, atypical location of the initial brain inflammation (such as the brainstem), delayed seizure onset (i.e. seizures beginning several months after the development of progressive neurological deterioration and hemispheric atrophy), and cases with dual pathology (RE plus low grade tumour, cortical dysplasia, tuberous sclerosis, vascular abnormalities or old ischemic lesions).

There are also rare reports of patients with RE in whom seizures were relatively well controlled with antiepileptic drugs or focal resections, and in whom the neurologic status stabilized spontaneously before the development of major neurological deficits. In his review of patients who underwent temporal resections for intractable focal seizures, Laxer found five patients (3.8 per cent of a series of 160 patients) with what he thought was a benign, focal, non-progressive form of Rasmussen encephalitis.[10] A recent article describes three patients who developed childhood or late onset RE with a relatively non-progressive form of the disorder.[11] Cases such as these appear to confirm Theodore Rasmussen's suggestion that the clinical spectrum of RE may be wider than first thought and that there might be milder and less progressive focal forms of the disease.[12]

Current issues in the treatment of RE

The optimal treatment of RE is unclear and controversial. Hemispherectomy—surgical removal or disconnection of the affected hemisphere—is widely considered to be only real 'cure' for RE. Although the operation causes severe deficits (spastic hemiplegia and loss of fine motor hand movements on the contralateral side, homonymous hemianopia to the contralateral side, and aphasia if the dominant hemisphere is affected), this may be preferable to ongoing seizures and the consequences of the disease itself.

In the last few years, however, a number of promising medical treatments have emerged (see pages 9 to 10). While none have yet been proven to control the disease in the longer term, and none provide adequate seizure relief to all patients, the existence of new options for medical management of the disease has greatly increased the complexity and difficulty of clinical decision-making associated with RE.

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9 Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement, *Brain*, 2005; 128:454-471.
10 Laxer KD. Temporal lobe epilepsy with inflammatory pathologic changes. In: Andermann F (ed), Chronic encephalitis and epilepsy, Rasmussen's syndrome. Stoneham MA, Butterworth-Heinmann, 1991: 135–140.
11 Gambardella A, Andermann F, Shorvon S, Le Piane E and Aguglia U. Limited chronic focal encephalitis: another variant of Rasmussen syndrome? *Neurology*, 2008; 70: 374-377.
12 Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis, *Neurology*, 1958; 8: 435-45.

Notwithstanding recent therapeutic advances, some experts argue that hemispherectomy should be performed as early as possible after diagnosis, in anticipation of the disease's inevitable consequences.[13] This viewpoint is supported by evidence that the best outcomes following hemispherectomy occur in younger children and when the operation is performed before the undiseased hemisphere has been damaged by seizures and drugs. Indeed, children with RE can make a remarkable recovery from hemispherectomy and many are able to function well in everyday life.

In practice, however, few neurology centres advocate for hemispherectomy until the disease has already caused marked physical deficits. The exceptions to this are cases in which seizures are life-threatening, where there is very rapid deterioration, and/or where numerous alternative therapies have been tried without success. Apart from the obvious trauma involved in removing a brain hemisphere from patients with highly preserved functioning, clinicians and families must weigh the 'benefits' of hemispherectomy against the evidence for:

- The effectiveness of recently identified forms of immunotherapy in significantly slowing progression of the disease and associated deficits, particularly the cognitive decline usually associated with RE.
- The possibility that further advances in immunotherapy will lead to effective non-surgical treatments for RE within the next few years.
- Identification of less progressive forms of the disease, as discussed earlier.

Additionally, there are some RE patients—for example, older teenagers and adults with dominant hemisphere disease—for whom hemispherectomy would be considered only in the most extreme circumstances. Hemispherectomy is also unsuitable for the small number of RE patients with bilateral disease.

A recent article discusses the difficulties involved in clinical decision-making for RE patients.[14] It describes an increasingly common scenario in which immunotherapy has stopped the patient's functional decline but not the frequent, handicapping seizures, which the patient may have endured for years. Such a situation often leads the treating clinician into a therapeutic dilemma: hemispherectomy is not favoured because of the inevitable postoperative functional deficits; but there is a real risk that the drugs used to delay progression of the disease may not work (or be tolerated) indefinitely and may delay definitive surgical treatment beyond the time when an optimal outcome could be expected.

13 See Reply to Daniel, authors' reply to Roy T Daniel's correspondence regarding their article (Granata T et al, Experience with immunomodulatory treatments in Rasmussen's encephalitis) published in *Neurology*, 2003; 61: 1807–1810.
14 Bien CG and Schramm J. Treatment of Rasmussen encephalitis half a century after its initial description: promising prospects and a dilemma, *Epilepsy Res.*, 2009, 86 (2-3):101-12.

Need for further research

RE is a devastating disease, and uncertainly about what course of action will provide the best outcomes adds to the distress experienced by patients, their families and clinicians. To obviate the therapeutic dilemmas currently associated with RE, and assist patients who are poor candidates for hemispherectomy, there is a pressing need for further research to discover a cure—or at least an effective medical treatment regime that can be used on a long-term basis without unacceptable toxicity.

Research on RE suffers from the limitations of other 'orphan' diseases. Studies are confined to a few centres worldwide, and are almost always based on small samples of patients. Natural variability in the course and pathophysiology of RE makes it particularly difficult to interpret the results of research based on small case series. Added to this, there has been limited collaboration between neurologists and immunologists in relation to what is now understood to be an autoimmune disease.

However, buoyed by recent partial successes with new immunotherapies for RE and advances in neuroimmunology generally, some experts are optimistic about the potential for further breakthroughs in the treatment of the disease. As well as relieving the suffering of RE patients, there are indications that such breakthroughs could have implications for a much larger group of epilepsy patients. Recently published studies indicate that active neuroinflammation and marked cellular injury occurs in paediatric epilepsy of diverse etiologies.[15] This suggests that immunomodulation and neuroprotective therapies found to reduce inflammation in RE might be used to prevent intractable epilepsy and neurological morbidity in a range of other conditions.

The remainder of this paper outlines some preliminary ideas for research to improve current understanding and treatment of RE. The author is not a doctor or a scientist, so the ideas are broad rather than specific. They are based on three key strategies:

- Research into the pathophysiology of RE.
- Ongoing evaluation of evidence for RE therapies.
- Reviewing the potential use in RE of current and emerging therapies for other autoimmune conditions.

15 Choi J, Nordli DR Jr., Alden T, DiPatri A Jr., Laux L, Kelley K, Rosenow J, Schuele SU, Rajaram V and Koh S. Cellular injury and neuroinflammation in children with chronic intractable epilepsy (Abstract), *Journal of Neuroinflammation*, 2009; 6:38.

Strategy 1: Research into the pathophysiology of RE

Background

Attempts to understand the cause of RE have naturally led to pathological examination of brain tissue removed from patients with the disease. This typically shows inflammatory changes with perivascular cuffing in both grey and white matter, glial nodules, areas of chronic spongy degeneration, and gliosis.[16] The vast majority of inflammatory cells involved in RE are T cells; in fact, they are cytotoxic CD8+ lymphocytes, which have been shown to attack neurons and astrocytes.[17]

The pathology is not uniform at all stages of the disease. Robitaille[18] divided RE brain specimens into four groups that roughly corresponded to disease duration. Group 1 (which he termed 'active disease') revealed inflammation with numerous microglial nodules, perivascular round cells and glial scarring. Group 2 ('active and remote disease') encompassed brain tissue showing several microglial nodules, with perivascular round cell cuffs and at least one gyral segment of complete necrosis. Group 3 ('remote disease') included cases displaying neuronal loss and gliosis with moderately abundant perivascular round cells and few microglial nodules. Finally, group 4 ('non-specific changes') showed no or few microglial nodules, but there was neuronal loss and mild perivascular inflammation combined with various degrees of gliosis and glial scarring.

A second pathology, such as cortical dysplasia, vascular malformations or ganglioglioma, is found in approximately 10 per cent of patients with RE. Researchers have speculated that a breakdown of the blood-brain barrier might bring about the development of chronic encephalitis by increasing the risk of a viral infection or by inducing an abnormal immune response.[19] (Alternatively, seizure discharges themselves may damage the blood–brain barrier).

The pathological changes and clinical features seen in RE led to the suggestion that the condition is caused by a viral infection, but efforts to detect viruses in brain specimens from RE patients have produced conflicting results. A number of studies have identified viruses, notably Epstein-Barr virus (EBV) and cytomegalovirus (CMV), in the brains of at least some of their samples of RE patients, and there are isolated reports of improvement, even long-term remission, in patients treated with antivirals early in the course of the disease.[20] However, other studies have failed to replicate these results.

16 Hart Y. Rasmussen's encephalitis, *Epileptic Disorders*, 2004; 6: 133–144.
17 Vining EPG, Struggling with Rasmussen's Syndrome, *Epilepsy Currents*, 2006; 6 (1): 20–21.
18 Robitaille Y. Neuropathologic aspects of chronic encephalitis. In: Andermann F, editor. Chronic encephalitis and epilepsy. Rasmussen's syndrome. Boston: Butterworth-Heinemann; 1991: 79–110.
19 Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, Lassmann H, Mantegazza R, Villemure J.-G, Spreafico R and Elger CE. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: A European consensus statement, *Brain*, 2005; 128: 454–471
20 Mclachlan RS; Levin S, and Blume WT. Treatment of Rasmussen's syndrome with gancyclovir, *Neurology*, 1996; 47 (4):925–928.

While a viral trigger for RE certainly has not been ruled out, it is now clear that an autoimmune response is important in the pathogenesis of the disease. The evidence for this has been presented in numerous review articles, including a 2005 'consensus statement' by a group of European experts.[21] One strand of evidence suggests that RE is an antibody-mediated immune response directed to antigens of resident brain cells. Antibodies to subunit 3 of the AMPA receptor (GluR3 antibodies) were at one stage believed to dominate pathogenesis, but subsequent work showed that not all RE patients have these antibodies. Nevertheless, the (temporary) effectiveness of plasmapheresis and immunoadsorption even in RE patients without GluR3 antibodies suggests that non-GluR3 directed antibodies may contribute to the pathogenesis in some patients. According to the latest review article by the Bien group, there is recent evidence that some RE patients have antibodies to the neuronal alpha7 acetylcholine receptor and to the presynaptic protein Munc18-1.[22]

Most current work, however, focuses on the role of T-lymphocytes (and the supporting role of B-lymphocytes) in RE. This work is reviewed in a recent article by Schwab and colleagues, which also presents the findings of new analyses on brain and peripheral blood samples from 14 RE patients.[23] The authors claim that their work strongly supports earlier suggestions of 'an antigen-driven MHC class-1 restricted, CD8+ T cell mediated attack against neurons and astrocytes in the central nervous system dominating the pathogenesis in RE.' This has been shown in many other autoimmune diseases. The Schwab group believes that its findings hint towards ongoing exposure to an as-yet-unknown antigen or antigens, which may be an auto antigen or virus residing within the CNS. They conclude that 'further work is warranted to characterise the nature of the recognised antigenic structure(s) by pathogenic T-cell clones.'

Directions for future research

Further study of brain tissue from patients operated on for RE is a very promising area of investigation. As noted above, it is likely that cytotoxic T lymphocytes recognize some specific antigen or antigens in RE patients' brains. Currently, the target of this attack remains unknown, but identification of the antigen/s could open up the way to more specific forms of immunotherapy and possibly a cure for the disease.

Investigations into the immunology and pathophysiology of RE have been hampered by the absence of large scale studies and lack of consistency in the methods used to identify potentially pathogenic agents. Currently, active research on the pathophysiology of RE is occurring at a small number of neurology centres and associated universities worldwide.[24] Many more centres can and do test brain samples from individual RE patients, with varying levels of capability and sophistication. However, most centres see only a few new cases of RE each year, so even when formal studies are based on collaboration between small groups of centres, it is rare for them to include more than 12–15 patients.

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21 Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement, *Brain*, 2005; 128:454-471.
22 Bien CG and Schramm J. Treatment of Rasmussen encephalitis half a century after its initial description: promising prospects and a dilemma, *Epilepsy Res.*, 2009, 86 (2-3):101-12.
23 Schwab N, Bien CG, Waschbisch A, Becker A, Vince GH, Dornmair K and Wiendl H, CD8+ T-cell clones dominate brain infiltrates in Rasmussen's encephalitis and persist in the periphery, *Brain*, 2009: 132; 1236–1246.
24 Reports accessible to the general public on the internet suggest that there is an active program of work occurring at the University Hospital at Bonn in Germany (sometimes in collaboration with the Universities of Munich, Wurzberg and Vienna). Some specific work on RE is also occuring at Oxford University in England, and Johns Hopkins University and the California Pacific Medical Centre in the United States. There may be others as well.

Larger-scale collaboration between centres is needed to advance our understanding of RE. The ability to conduct research based on larger samples is especially important given strong indications, based on variability in the clinical course and brain pathology of patients, that a uniform process does not take place in all individuals with RE or at all stages of the disease. However, there are at present no data to meaningfully distinguish subgroups of patients, especially in regard to therapeutic strategies that might be appropriate in different circumstances.

The development of a centralised 'tissue bank' could be a key strategy to advance primary research into the pathophysiology of RE. This would allow brain tissue from patients across many centres to be collected and analysed in a consistent manner and using the most advances techniques, including emerging techniques for identifying the target antigens of autoreactive human T and B cells.[25]

The primary objective of the RE brain bank would be to co-ordinate the collection, storage and use of brain tissue from people with RE who have undergone biopsy or hemispherectomy. The bank would require one centre to establish the facilities and processes to enable other centres to send brain specimens from RE patients. The lead centre would need to actively promote the bank, provide guidelines on the preparation and transport of samples, and develop protocols for the range of analyses to be performed and the methods to be used. As an incentive for other centres to participate in the initiative, clinicians providing samples could be given access to the pathology findings relating to their own patients and aggregated data, perhaps provided via a secure internet site, on the overall research program.

Strategy 2: Ongoing evaluation of evidence for RE therapies

Background

Despite the increasingly complex clinical decision-making associated with the disease, there are no established clinical guidelines for RE. The 2005 European consensus statement on RE is a very good starting point, but it provides little guidance about how to rank the various immunotherapies it describes. The statement is also somewhat out-of-date, as it does not take into account advances made in the last five years.

In the absence of an accepted therapeutic strategy, management of the disease varies greatly between clinicians and hospitals. Current approaches to both diagnosis and treatment tend to be ad hoc, and do not necessarily reflect the latest research findings on the importance of early diagnosis and intervention, or available information about the effectiveness of various therapies.

Reports on the outcomes of various drugs that suppress the immune system and therapies that modulate the function of the immune system are available. A brief summary of these therapies, based on the author's understanding of published reports and personal communication with clinicians, appears below. The various reports on the treatments are usually based on individual patients or small case series.

[25] Dornmair K, Meinl E, and Hohlfeld R. Novel approaches for identifying target antigens of autoreactive human B and T cells, *Seminars in Immunopathology*, 2009, 31 (4): 467–477.

Antiviral therapy

There are two reports showing improvement in patients treated with the antivirals gancyclovir or zidovudine.[26] Although definite improvement was documented in four of the five patients involved, no further reports have been published.

Plasmapheresis and immunoadsorption

The majority of RE patients show transient responses to plasmapheresis (plasma exchange) and immunoadsorption, which are treatments that remove circulating antibodies from the bloodstream. However, because of the lack of long-term efficacy, the potential complications, and the expense of these treatments, they are usually regarded as adjunctive therapies to be used in cases of acute deterioration and very frequent seizures.

Intravenous immunoglobulin

There are reports of striking improvements in seizure control, hemiparesis and cognition using high dose human immunoglobulin (IVIg) administered for several months or more.[27] However, the evidence for a long-term is much less clear-cut. Some centres have found little success with IVIg in the absence of steroids.[28] A randomised trial comparing IVIg to tacrolimus (see below) is underway at the University Hospital in Bonn.[29]

Tacrolimus

Tacrolimus, an agent directed at T cells, was tested in an open study that demonstrated significantly reduced progression of hemispheric atrophy and hemiparesis in patients treated with this agent compared to untreated patients.[30] However, tacrolimus had no effect on seizure frequency.

Steroids

Prednisolone/prednisone has been reported to have beneficial effects on seizures and neurological functions in several series, particularly when started early in the disease course. However, high doses are usually needed (either alone or in association with other agents such as IVIg) and the frequent occurrence of complications makes this difficult to maintain on a long-term basis.

Azathioprine

There is a brief report on six RE patients treated with the immunosuppressant azathioprine.[31] Four of the children showed improved seizure control and reduced progression of the disease over a period of five years, while two had no response.

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26 See Mclachlan RS; Levin S, and Blume WT. Treatment of Rasmussen's syndrome with gancyclovir, Neurology, 1996; 47 (4):925–928 and DeToledo JC and Smith DB. Partially successful treatment of Rasmussen's encephalitis with zidovudine: symptomatic improvement followed by involvement of the contralateral hemisphere, *Epilepsia*, 2005; 35 (2): 352–355.
27 Leach JP, Chadwick DW, Miles JB, and Hart IK. Improvement in adult-onset Rasmussen's encephalitis with long-term immunomodulatory therapy, *Neurology*, 1999; 52: 738.
28 Personal communication (31 August 2008) with Professor Helen Cross, Head of Neurosciences Unit, UCL-Institute of Child Health, United Kingdom.
29 Efficacy of tacrolimus and i.v. immunoglobulins in Rasmussen encephalitis, http://clinicaltrails.gov/ct2/show/NCT00545493
30 Bien, CG, Gleissner U, Sassen R, Widman G, Urbach H and Elger CE. An open study of tacrolimus therapy in Rasmussen encephalitis, *Neurology*, 2004; 62: 2106–2109.
31 Shah S, Varadkar S, and Cross JH. The role of azathiaprine in Rasmussen's syndrome, *Developmental Medicine Child Neurology*, 2005; 47 (s101): 18.

Cyclophosamide

Some American centres are using high-dose cyclophosphamide (cytoxan) to treat patients who are unsuitable for hemispherectomy. A number of patients have been treated in this way at Johns Hopkins, with mixed results.[32] However, the long-term risks associated with this drug would appear to be significant.

Intraventricular interferon-alpha

In a report based on a single case, a six-week course and later a six-month course of intraventricular (i.e. injected into the brain ventricles) interferon-alpha almost totally suppressed previously refractory seizures in a four year old RE patient.[33] No follow-up information or additional studies have been reported.

Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody that targets B lymphocytes. It is approved for treatment of non-Hodgkin's lymphoma and rheumatoid arthritis.

An unpublished pilot study, based on a multi-centre, open label, uncontrolled trial based at the California Pacific Medical Research Centre, investigated the safety, tolerability and efficacy of rituximab in the treatment of RE.[34] Of the nine patients treated, all except one showed some improvement in seizure severity and frequency (50–100 per cent decrease) with three becoming seizure free (including two with epilepsia partialis continua). All eight patients who continued in the trial demonstrated improved global assessments with some showing dramatic improvements in cognitive and/or motor function. None demonstrated further progression of their disease either clinically or radiographically. All the infusions were well tolerated without clinical or laboratory evidence of serious side effects. (However, there are reports of serious adverse effects associated with the use of rituximab in some other autoimmune diseases).

An additional case report from Germany reported complete seizure freedom in a 20-year patient treated with rituximab.[35]

Although these results are exciting, there is no data on how long the efficacy of rituximab is sustained—and hence its value relative to hemispherectomy for children who are good candidates for the surgery. In 2008, when the findings of the pilot study were made available, the patients had been followed post treatment for three to 22 months, with average 10.2 months. Subsequent contact with the principal investigator indicated that the patients have continued to do well, but the author has heard via personal contacts of two other children treated in the United States and Canada for whom the improvement lasted only a few months.

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32 Personal communication (28 August 2008) with Professor Eileen Vining, Johns Hopkins University School of Medicine, Baltimore, United States.
33 Dabbagh O, Gascon G, Crowell J, and Bamoggadam F. Intraventricular interferon-alfa stops seizures in Rasmussen's encephalitis: a case report, *Epilepsia*, 1997; 38(9): 1045–9.
34 A pilot study in the use of rituximab in the treatment of chronic focal encephalitis, http://clinicaltrials.gov/ct2/NCT00259805. The results reported are based on personal communication with the principal investigator, Dr Ken Laxer, on 3 June 2008.
35 Thilo B, Stingele R, Knudsen K, Boor R, Bien CG, Deuschl G and Lang N. A case of Rasmussen encephalitis treated with Rituximab: case study, *Nature Reviews Neurology*, 2009; 5: 458–462.

There are unanswered questions about the optimal protocol for use of rituximab in RE. For example, in the German patient described above, excellent results were obtained using immunoadsorption prior to the rituximab infusion, but this is not part of the protocol now being used in a number of centres in the United States, Canada and, very recently, Australia. There is also a need to consider whether rituximab should be given in conjunction with IVIg, as reports based on its use in other conditions suggest that IVIg improves the safety and effectiveness of rituximab.[36]

Directions for future research

Although a number of small clinical trials have been completed or are underway, there is little information on the optimum combination, dosing, or duration, or the ongoing effectiveness of currently used RE treatments. There a strong need for evaluative data (particularly in relation to different sub-groups of patients) based on larger sample sizes and longer term follow up of RE patients. Information about long term outcomes is particularly critical to decisions about whether medical or surgical interventions will provide the best results for individual patients.

Collaboration between centres would enable a more rigorous and efficient approach to assessing the safety and efficacy of RE interventions than has been possible to date. Strategies that could provide a platform for collaborative research and ongoing evaluation of RE treatments are discussed below.

Clinical guidelines

Based on available published and unpublished information on the outcomes of current RE interventions, a panel of experts (ideally representing major neurology centres across the world) could develop an agreed position paper or clinical guideline on the treatment of the disease. This could include:

- *Guidelines to facilitate early recognition and diagnosis of RE*. The 2005 European consensus statement provides useful criteria but probably underestimates the difficulties of early diagnosis based on clinical criteria alone in cases where the disease is very slowly progressive. Given increasing recognition of the importance of early diagnosis and treatment, there may be a need for stronger recommendations about the value of early biopsy in cases of suspected but unconfirmed RE.
- *Guidelines for management of suspected but unconfirmed RE cases*. Again, given the importance of early intervention, the guidelines should address whether low-risk immunotherapies, such as IVIg (or antivirals if a viral situation is suspected), should be commenced even before the diagnosis is confirmed.
- *Guidelines for management of confirmed RE cases*. This would provide:
    - Risk/benefit information, based on available evidence, of key immunotherapies that could be helpful at various stages of the disease.
    - An opinion on whether more aggressive immunotherapies (which currently tend to be avoided until their risks are outweighed by the severity of the disease) should be considered early in the disease course—based on increasing recognition that some severe neurological autoimmune diseases are amenable to cure only in their early stages.

36 Ar A et al. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin, New *England Journal of Medicine*, 2006; 355: 1772–1779.

- An opinion on the optimal (set of) anti-seizure medication/s, and any supplementary immunotherapies, to be used in conjunction with the above.
- A clinical pathway based on clear decision-support criteria, to assist in identifying exit points from particular medical treatments and progression to either more aggressive immune interventions or to hemispherectomy. The pathway should of course take into account individual variables such as the patient's age, disease lateralization, general health, progression rate, neurological and neuropsychological impairment, and personal/family preferences.
- Recommendations for the collection of patients' demographic and clinical data about the patient, including key outcome measures.

Multi-centre registry

An agreed set of outcome measures, as proposed above, could contribute to the development of multicentre registry of RE patients. Participating centres would accumulate and track standardized information about children with RE and enter de-identified data into a secure web-based database, which would be maintained by a host centre. Collection and sharing of the medical and surgical histories of a large number of children RE would provide a rich source of information about the relative success of different interventions.

The registry would provide data for comparative clinical studies of RE treatments, and would enable timely identification of new therapies that show promise in individuals or case series, and which could be considered for larger trials. Table 1 provides a summary of the European consensus statement's recommendations concerning future research on therapies for RE, which could inform the development of collaborative research projects.

Table 1: Summary of recommended principles for future therapeutic research in Rasmussen's encephalitis[37]

1. Any kind of valid therapeutic report should provide information about the long-term outcome of the patients treated, i.e. it should cover a follow-up period of at least one or two years.
2. Given the variability of the RE course, only studies on patient cohorts (not single cases) will provide relevant new information.
3. Placebo controlled studies are no longer conceivable in RE. A prospective randomised comparison of surgical and an immunotherapeutic treatment is also unacceptable as there will be only rarely a situation in which hemispherectomy and long-term immunotherapy are equally beneficial for the patient.
4. For any study of a treated patient cohort, a control group will be necessary. As a minimum requirement, an adequate historical control group should be retrospectively analysed.
5. While logistically difficult, the ideal type of study would be a controlled clinical trial using prospective, randomized, multi-centre methodology. This would be based on randomized long-term comparison of currently accepted treatments to each other or of a 'new' therapy to one of the accepted regimens. A double-blind design may not be feasible in such a long-term study, especially if a drug like IVIg is tested.
6. Because of the non uniform activity of the pathological process during the disease course and in different age groups, only patients at similar disease stages and of similar ages should be compared.
7. The most relevant and assessable clinical measures of treatment efficacy are degree of hemiparesis and seizure frequency. MRI assessment of the degree of hemiatrophy might further enhance the validity of the study. Periodic testing of neuropsychological functions or health-related quality of life may be further options.
8. Regular follow-up visits and pre-defined exit criteria (e.g. a certain increase in the degree of hemiparesis) are desirable. This would permit a timely consideration of hemispherectomy or change of immunotherapy according to an established pathway if a trial drug fails to stop the disease progression.

37 From Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement, *Brain*, 2005; 128:454-471.

Strategy 3: Reviewing the potential use in RE of current and emerging therapies for other autoimmune conditions

Background

An important strategy in identifying potential new therapies for RE will be to examine treatments that are being developed and used in more common autoimmune neurological diseases (and possibly other autoimmune conditions). For example, multiple sclerosis, to which RE has been compared,[38] is the target of extensive research and a range of promising new treatments.

Many of the therapies discussed in the previous section in relation to RE are also being used or trialed for a range of other disorders. Besides these, a range of other technologies and treatments are thought to have actual or potential applicability to neurological autoimmune diseases. Some of these are noted below.

Monoclonal antibodies

The development of targeted approaches in immunomodulation, acting on specific molecules involved in the pathological process, is widely considered to be the way of the future in the treatment of autoimmune diseases.

Because of their unique specificity for different molecules, monoclonal antibodies (mAbs) are promising treatments for a range of diseases. Although the early experience with monoclonal antibodies was disappointing, the past five years have seen a major change of fortune, with numerous mAbs now approved for clinical use in a range of conditions. These include reagents against cancer, transplant rejection, antiviral prophylaxis and a variety of immunological conditions such as rheumatoid arthritis, Crohn's disease and MS.

A recent article reviews the monoclonal antibodies that are approved, or being trialed, for the treatment of MS.[39] As well as rituximab, these include natalizumab (Tysabril), alemtuzumab, ocrelizumab, daclizumab (Zenepax) and ustekinumab. The authors conclude that early, effective treatment with monoclonal antibodies has the potential to prevent or delay disability in MS. The mAbs reviewed in the article work in varying ways, targeting different aspects of the disease process. Careful examination of these therapies (and perhaps mAbs being used for some other autoimmune conditions) may be warranted to assess their suitability for trial in RE patients.

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38 See Vining EPG. Struggling with Rasmussen's syndrome, *Epilepsy Currents*, 2006; 6 (1): 20–21. According to Professor Vining, the pathologic findings in RE, in which abnormal and normal tissue can be found in juxtaposition to each other, 'force consideration of mechanisms postulated for multiple sclerosis and post infectious encephalomyelitis.' Parallels between RE and paraneoplastic encephalitis have also been noted.

39 Helliwell, CL and Coles AJ. Monoclonal antibodies in multiple sclerosis treatment: current and future steps, *Therapeutic Advances in Neurological Disorders*, 2009; 2(4): 195–203.

Stem cell technology

Stem cell-based therapies offer many exciting possibilities for the development of novel treatments, and perhaps even cures, for autoimmune diseases.

Most experts would agree that the potential the technology has yet to be fully realised, but there is now clear evidence that stem cell therapy has led to long-term remission, if not complete cure, in the early stages of some severe neurological autoimmune diseases, including MS[40] and chronic inflammatory demyelinating polyneuropathy.[41] Stem cell therapy for autoimmune disease focuses on destroying, and then regenerating, only the immune component of the bone marrow: this makes the procedure safer and less toxic than chemotherapy/stem cell transplantation for cancer. A 2007 review of approximately 1,000 patients who received an autologous stem cell transplant for a range of severe autoimmune diseases concluded that 'many patients have experienced long-term disease-free remissions and immune reconstitution studies have shown in some cases that a "resetting" of autoimmunity is possible.'[42] The review also found that the initially high treatment-related mortality had reduced significantly in recent years.

There is one published report of an RE patient who underwent immune ablation and stem cell reconstitution with CD34+ haematopoietic stem cells from her identical twin.[43] This resulted in a remission period of only a few months, leading the researchers to conclude that the relevant T-cells residing in the CNS were not sufficiently eradicated by the immunablative regimen.

RE is among the autoimmune neurological diseases eligible for a current phase 1/11 trial of autologous stem transplant following high-dose immunosuppressive therapy.[44] It is not known whether any RE patients have enrolled in the trial, which also accepts patients with a range of other diseases, including MS.[45] The estimated completion date for the trial is December 2013, though preliminary findings may be available before that time.

The immediate and longer term risks of stem cell therapy are major considerations, especially for pediatric patients. However, the development of more targeted immunablative therapies may enable stem cell procedures to be undertaken more safely and effectively in the future. And while the risks and costs of these technologies cannot be discounted, they need to be weighed against the high personal, social and medical costs associated with RE.

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40 Fagius J, Lundgren J, and Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation, *Multiple Sclerosis*, 2009; 15 (2): 229–237.
41 Vermeulen M and Van Oers MH, Successful autologous stem cell transplantation in a patient with chronic inflammatory demyelinating polyneuropathy, *The Journal of Immunolo*gy, 2009; 182: 6569–6575.
42 Passweg J and Tyndall A. Autologous stem cell transplantation in autoimmune diseases, *Seminars in Hematology*, 2007; 44(4): 278–85.
43 Schwab N, Bien CG, Waschbisch A, Becker A, Vince GH, Dornmair K and Wiendl H, CD8+ T-cell clones dominate brain infiltrates in Rasmussen's encephalitis and persist in the periphery, *Brain*, 2009: 132; 1236–1246.
44 Combination chemotherapy and antithymocyte globulin followed by stem cell transplant in treating patients with severe autoimmune neurologic diseases that did not respond to previous therapy, Clinical trial sponsored by the Fred Hutchinson Cancer Research Centre, National Cancer Institute, United States, http://clinicaltrials.gov/ct2/show/NCT00716066.
45 Personal communication with Richard Nash, the principal investigator in the trial, on 16 May 2009, indicated that no RE patient had been recruited at that time.

Suppression of microglia-mediated inflammation

The inflammatory response in many neurological diseases, including RE, is thought to be partly mediated by activated microglia, the resident immune cells of the CNS. In recent research assessing Iba1-immunolabelled microglial activation in the neocortex of eight RE patients, microglial reactivity was increased in severely affected areas compared with minimally affected areas of RE. [46] (It was also increased in RE patients compared to patients with cortical dysplasia and tuberous sclerosis complex; however, there was no qualitative association of Iba1 immunolabelling with the presence of CD8+ cytotoxic T-cells and no statistical association with clinical epilepsy variables, such as seizure duration or frequency). The research suggests that Iba1 is an excellent marker for detecting extensive microglial activation in RE patients and, by association, the extent of active RE.

Suppression of microglia-mediated inflammation has been considered as an important strategy in neurodegenerative disease therapy. Several anti-inflammatory drugs have been shown to repress the microglial activation and to exert protective effects on the brain.[47]

Current work includes research on the possible neuroprotective effects of the antibiotic minocycline against progression of a group of neurodegenerative disorders including MS, rheumatoid arthritis (RA), amyotrophic lateral sclerosis (ALS), Huntington's disease, and Parkinson's disease.[48] It is thought that minocycline exerts neuroprotective effects independent of its anti-inflammatory properties. A 2007 pilot study reported the impact of minocycline on clinical and MRI outcomes in MS patients over 24 months of open-label minocycline treatment.[49] Despite moderately high relapse rates prior to treatment, no relapses occurred between months 6 and 24 of the study. The only patient with gadolinium-enhancing lesions on MRI at 12 and 24 months was on half-dose minocycline. The clinical and MRI outcomes in this study were supported by systemic immunological changes. It is not known whether the results of this study have been validated in more recent research.

Drugs targeting the blood-brain barrier

Changes in the blood-brain barrier are thought to be critically important to the development of many neurological disorders. The blood-brain barrier is therefore a key site for therapeutic intervention, as recently evidenced by the approval of the therapeutic monoclonal antibody natalizumab, which is directed against alpha-4-beta-1-integrin and inhibits the influx of autoaggressive T cells into the CNS.[50] Other therapies based on restricting the migration of immune cells across the blood brain barrier are also being explored.

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46 Wirenfeldt M, Ryan C, Tung S, Bottini A, Mathern GW, Vinters HV. Increased activation of Iba1+ microglia in pediatric epilepsy patients with Rasmussen's encephalitis compared with cortical dysplasia and tuberous sclerosis complex, *Neurobiological Diseases*, 2009; 34 (3):432-40.

47 Thameem Dheen S, Kaur C, and Ling E-A. Microglial activation and its implications in the brain diseases, *Current Medicinal Chemistry*, 2007; 14 (11): 1189-1197.

48 Maier K, Merkler D, Gerber J, Taheri N, Kuhnert AV, Williams SK, Neusch C, Bähr M, Diem R, Multiple neuroprotective mechanisms of minocycline in autoimmune CNS inflammation, *Neurobiological Diseases*, 2007, 25 (3): 514–25.

49 Zabad RK, Metz LM, Todoruk TR, Zhang Y, Mitchell JR, Yeung M, Patry DG, Bell RB, Yong VW, The clinical response to minocycline in multiple sclerosis is accompanied by beneficial immune changes: a pilot study, *Multiple Sclerosis*, 2007; 13 (4): 517–26.

50 Engelhardt B and Sorkin L. The blood-brain and the blood-cerebrospinal fluid barriers: function and dysfunction, *Seminars in Immunopathology*, 2009; 31 (4): 497–511.

Gene therapies

Many experts believe there is a genetic basis for all autoimmune disease, since under normal circumstances the body does not attack its own tissue. There is evidence that certain gene patterns predispose people to developing particular autoimmune diseases, such as MS. In addition to inherited genes, autoimmune disease may be associated with random genetic mutations caused by environmental factors, including viral or infectious agents.

Mutations in certain genes may be also responsible for hyperexcitability in the brain, and hence the development of epilepsy. For example, it is now known that many types of epilepsy are the result of inherited changes in ion channels, which are proteins on the surface of brain cells that regulate the flow of ions in and out of the cell.[51] Knowledge that many types of epilepsy have a significant genetic component has lead researchers to look deeper into the genetic mechanisms involved in seizure disorders and the genes involved in the normal brain's protective mechanisms for inhibiting epilepsy.

Although data from extensive research has led to accumulating knowledge on the genetic mechanisms associated with many autoimmune and epileptic diseases, their direct clinical applications have been sparse. However, clinical successes have been increasingly reported in the last five years. For example, in November of 2009, the journal *Science* reported that researchers succeeded in halting a fatal brain disease, adrenoleukodystrophy, using a viral vector to deliver the gene for the missing enzyme.[52]

Probably more significant for diseases such as RE are advances in biotechnology that have laid the groundwork for using gene therapies to target specific molecules involved in the pathogenesis of autoimmune and inflammatory conditions. For example, research in Japan suggests that T cell receptor (TCR) gene transfer may lead to antigen-specific immunotherapies, with researchers confirming the efficacy of TCR gene therapy in animal models of systemic autoimmune disease and arthritis.[53] Researchers at Stanford University have developed a patented DNA vaccine designed to prevent or reverse T cell pro-inflammatory responses and have used this technology to successfully protect against a mouse model of MS. Such applications of gene therapy are still in their infancy but the pace of breakthroughs continues to accelerate, moving gene therapy closer towards mainstream medicine.

51 Mulley JC, Scheffer, IE, Petrou S; Berkovic, S. Channelopathies as a genetic cause of epilepsy, Current Opinion in Neurology, 2003; 16 (2): 171-176.
52 http://sciencenow.sciencemag.org/cgi/content/full/2009/1105/1
53 Fujio K, Okamura T, Okamoto A and Yamamoto K. T cell receptor gene therapy for autoimmune diseases, *Annals of the New York Academy of Sciences*, 2007, 2007; 1110: 222-232.

GABA

The neurotransmitter GABA is essential for regulating neuronal excitability throughout the CNS; many drugs for epilepsy work by increasing GABA levels. Building on previous work showing that GABA also has a role in the immune system, and appears to lower inflammation, Bhat et al[54] hypothesized that MS may be accelerated by low GABA levels. The authors report that immune cells produce GABA and that antigen presenting cells express functional GABA, suggesting that the immune system has the capacity to use GABA in signaling and modulation. The authors showed that mice with autoimmune encephalomyelitis, the experimental model of MS, benefited from increasing GABA levels and showed reduced paralysis. They concluded that the GABA system could represent a potential therapeutic target for MS and other autoimmune diseases.

Combination therapies

Some experts in MS consider that long-term management of this disease will be achieved through a combination of approaches rather than any specific drug.[55] Professor Eileen Vining, a researcher and clinician with a longstanding interest in RE, makes a similar point in relation to RE when she says 'we think we need to go after the microglia, not just the lymphocytes'.[56] The challenge in RE will be to identify the most effective and safest combination of therapies and to target these appropriately at different stages of the disease (and possibly different patient sub-groups).

In considering combination therapies, the role of non-traditional complementary therapies should not be discounted. There are reports on the internet from parents of children with RE who have found beneficial effects on seizures from complementary therapies (as an adjunct to traditional antiepileptics and immunotherapies). One substance that is receiving serious attention from scientists is a drug derived from the hydrangea root, which has been used for centuries in traditional Chinese medicine. Researchers from the Program in Cellular and Molecular Medicine and the Immune Disease Institute at the Children's Hospital Boston, along with the Harvard School of Dental Medicine,[57] have shown that the drug contains a small-molecule compound known as halofuginone that inhibits the development of Th17 cells (immune cells recently recognized as important players in autoimmune disease) without altering other kinds of T cells involved in normal immune function. They have demonstrated that halofuginone reduces disease pathology in a mouse model of autoimmunity. Halofuginone is in clinical trials for scleroderma.

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54 Bhat R, Axtell R, Mitra A, Miranda M, Lock C, Tsien RW and Steinman L. Inhibitory role for GABA in autoimmune inflammation, *Proceedings of the National Academy of Science of the United States of America*, 2010, 107: 2580-2585; published online before print February 1, 2010.

55 See Per Soelberg Sorensen cited in Mallarkey, G. What are the therapeutic advances in neurology? Opinions from world experts, Therapeutic Advances in Neurological Disorders, 2008, 1(1) 5–12.

56 Personal communication (28 August 2008) with Professor Eileen Vining, Johns Hopkins University School of Medicine, Baltimore, United States.

57 Sundrud MS, Koralov SB, Feuerer M, Calado DP, Kozhaya AE, Rhule-Smith A, Lefebvre RE, Unutmaz D, Mazitschek R, Waldner H, Whitman M, Keller T, & Rao A. Halofuginone inhibits TH17 cell differentiation by activating the amino acid starvation response, *Science*, 2009; 324 (5932):1334–8.

Directions for future research

The above discussion suggests that it could be valuable to review therapies currently being used or trialed for other autoimmune conditions (and possibly some forms of cancer and organ transplantation) to identify approaches that could be predicted on theoretical grounds to have benefit in slowing or halting the progression of RE. This will require careful assessment of whether the drugs' mechanisms of action, safety and effectiveness would make them suitable for development or trial in relation to RE. (The recent development of an animal model of RE by researchers at the University of Montreal may be useful in testing new drug applications before they are trialed in humans with RE).[58]

Evaluating the potential usefulness in RE of new and emerging therapies for other autoimmune conditions is well beyond the grasp of those who are not expert in immunology. At a recent meeting between leading RE clinicians and parents of children with RE, it was agreed that the involvement of experts from a range of specialist disciplines, such as immunologists, molecular biologists, oncologists, pharmacologists and geneticists, could help speed progress in understanding and treating RE.[59]

Any dedicated primary or secondary research on RE should now routinely include the involvement of all relevant disciplines in addition to neurologists with expertise in neuroimmunology.

58 See website of Citizens United for Research in Epilepsy (CURE), www.cureepilepsy.org, accessed 18 January 2010.

59 Personal communication (11 December 2009) with Seth Wolberg, father of a child with RE, who met with leading experts in RE who were in Boston in December 2009 for the American Epilepsy Society's Annual Meeting.