Review article

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Rasmussen's encephalitis

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ABSTRACT – Rasmussen's encephalitis, a syndrome characteristically presenting in children with the onset of partial motor seizures followed by progressive hemiparesis and cognitive impairment, and accompanied by unilateral cerebral atrophy, was described nearly 50 years ago, yet the cause and optimum treatment remain unclear. Although it was originally presumed to have a viral aetiology, the possible roles of antibody-mediated mechanisms and more recently cell-mediated immunity in its pathogenesis have come under increasing scrutiny in the last ten years. These developments are discussed, together with a review of the clinical features. The advances in treatment which have accompanied these changes are also assessed.

KEY WORDS: Rasmussen's syndrome, chronic encephalitis, epilepsy, immunology

The syndrome of focal seizures due to chronic localised encephalitis was first reported in 1958 by Rasmussen *et al.* [1], who described intractable focal epilepsy presenting in childhood, usually in the form of focal motor seizures, associated with progressive hemiparesis and cognitive impairment. The condition was accompanied by progressive unilateral cerebral atrophy. Conventional antiepileptic drugs were unhelpful in treating the seizures, but the disease process appeared to be halted by hemispherectomy.

Pathological examination of the diseased brain showed inflammatory change with perivascular cuffing by round cells in both grey and white matter, glial nodules, areas of chronic spongy degeneration, and gliosis. This inflammatory picture, together with the observation that in two out of three children the onset of the illness was preceded by a minor episode of infection or inflammation within the preceding six months, led to speculation that an infective process might be responsible. Almost fifty years on however, the cause remains unknown, with an extensive search for infectious agents having largely given way to the suggestion that the disease has an autoimmune origin [2, 3].

Clinical course

Since the original description, more than one hundred further patients have been reported [4-9] and the inclusion of a number of patients with atypical features suggests that the clinical spectrum may be wider than first thought. The typical features of Rasmussen's encephalitis (RE) are onset in childhood (usually between the ages of 14 months and 14 years), the development of slowly progressive, neurological deterioration including hemiparesis, cognitive impairment, and dysphasia, where the dominant hemisphere is involved, radiological evidence of progressive, usually unilateral, cerebral atrophy, and a pathological picture suggesting a viral encephalitis [6]. In about 50% of patients an infectious or inflammatory episode has occurred within six months prior to the onset of the illness. Seizures are the most common initial symptom, with approximately one fifth of patients presenting with generalised or focal status epilepticus, one third with a generalised tonic

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clonic seizure and the others with partial seizures. Focal motor seizures occur in three quarters of patients during the course of the illness, and epilepsia partialis continua in more than 50%. Todd's paresis is common prior to the development of a fixed neurological deficit. Complex partial seizures with or without automatisms may occur.

Eventual hemiparesis is usual, occurring within a year of onset in about 40%. Most children show evidence of cognitive and behavioural deterioration shortly afterwards, progressing over a period lasting from months to ten years, with the median period of progressive neurological deterioration being three years [6]. Bien *et al.* [9] found a shorter period of acute disease characterised by increasing seizures and progressive hemiparesis, with a median duration of eight months. Any significant improvement in the seizure disorder usually only occurs after the development of major neurological deficit, and some authors dispute that the disease can "burn itself out" [7]. However, Bien's study [9], describing 13 patients, delineated three phases: an initial prodromal phase characterised by a relatively low seizure frequency and only rarely some degree of hemiparesis (median duration 7.1 months), a stage of acute disease, with frequent simple partial motor seizures and the development of hemiparesis, and a residual phase in which the hemiparesis remained stable, and seizure frequency decreased in all patients, one patient even becoming seizure-free.

Atypical clinical features

Since the original description, a number of atypical features have been described. The occurrence of uveitis prior to or in the early stages of the disease in a few patients [10, 11] was thought to lend support to an underlying viral aetiology, other causes of uveitis and meningoencephalitis being thought unlikely on clinical grounds. More recently, a movement disorder, in the form of chorea, athetosis or dystonia, has been reported as a presentation of RE [12-14]. Prominent atrophy of the caudate nucleus was reported in these patients in addition to the frontal and perisylvian atrophy characteristically seen in children with RE. Other variants have included brain stem encephalitis [15] with bilateral external ophthalmoplegia, diminished gag reflex and central hypoventilation ensuing two months after the development of left-sided focal motor seizures and left hemiparesis. A clinical picture emerges of alternating epilepsia partialis continua affecting both sides of the body independently and associated with severe psychomotor regression in two brothers, the children of consanguineous parents [16].

RE has also been reported in adults [17-20]. Hart *et al.* [20] described three distinct presentations in 13 adults developing refractory partial onset seizures, with histopathological features of RE. Five patients developed seizures in adulthood (aged 21-40 years), but otherwise had clinical features similar to those seen in children, though only three developed a hemiparesis or field defect and two had progressive cognitive impairment. The second group (five patients) developed seizures in adolescence, four developing hemiparesis or visual field defect over 3-15 years, while two experienced progressive cognitive impairment. In the third group, initial investigation at the time of presentation with seizures suggested the presence of a mass lesion, an inflammatory process being shown on biopsy. In one, the pathological appearances were atypical, with caseation and giant cells, although no alternative aetiology was identified.

The reported prognosis in adults has been rather variable: Gray [17] and McLachlan *et al.* [18] found more severe progressive neurological deficit than is typical in children, although the seizure severity and cognitive impairment were less severe, while the patients of Hart *et al.* had a more benign course. There is an increased incidence of bilateral disease [18, 20], and a tendency towards occipital involvement [21]. The occurrence of such atypical cases raises the possibility that RE may represent a spectrum of disease rather than a discrete entity, a suggestion echoed by Hennessy *et al.* [21], who described pathological changes typical of RE in two patients in whom temporal lobectomy was performed for the relief of long-standing temporal lobe epilepsy.

The diagnosis of RE can usually be made clinically, although other conditions such as cortical dysplasia [22, 23], tumour [24], cerebral vasculitis [25] and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [26] need to be considered. Diagnostic criteria suggested by Hart *et al.* [27], proposing the use of protocols for the medical treatment of this condition, were as defined below (A) and (B):

A. *Children who develop epilepsia partialis continua and meet at least one of the following criteria to suggest the diagnosis of chronic encephalitis:*

(1). progressive neurologic deficit at the beginning or after the onset of epilepsia partialis continua, but before the start of treatment;

(2). progressive hemispheric atrophy on CT, MRI, or both, with or without density or signal abnormalities,

(3). presence of oligoclonal or monoclonal banding on CSF examination, or

(4). biopsy evidence of chronic encephalitis.

B. *Children who do not have epilepsia partialis continua but do have focal epilepsy and biopsy evidence of chronic encephalitis. They may, in addition, meet criteria 1, 2 or 3.*

Pathological features

The gross pathological appearances described by Rasmussen in 27 patients undergoing surgery for chronic encephalitis were those of non-specific, atrophic or cicatricial brain changes [28]. The typical microscopic

appearances are also non-specific, features including perivascular cuffing by lymphocytes, glial nodules scattered throughout the grey and white matter, and later destructive changes appearing first as laminar necrosis and later spongy degeneration *(figure 1)*.

Four stages of the condition have been delineated by Robitaille [29]. Group 1, which he termed "active disease" includes specimens characterised by numerous microglial nodules, with or without neuronophagia, accompanied by perivascular round cells and glial scarring. The second group, labelled "active and remote disease", encompasses brain tissue showing several microglial nodules, with perivascular round cell cuffs and at least one gyral segment of complete necrosis and cavitation including full-thickness cortex. Specimens showing neuronal loss and gliosis with moderately abundant perivascular round cells and few microglial nodules fall into the group of "remote disease" (group 3), while group 4 ("non-specific changes") includes tissues with no or very few microglial nodules and mild perivascular inflammation, combined with various degrees of neuronal loss and glial scarring.

A second pathology, such as cortical dysplasia [30-32], vascular malformations resembling cavernous haemangiomata, astryocytoma [31], or ganglioglioma [33] has been found in approximately 10% of patients with RE [31]. In view of the rarity of RE it seems unlikely that this is coincidental, and it has led to speculation that the breakdown of the blood-brain barrier associated with the original lesion may have brought about the development of a chronic encephalitis either by increasing the risk of a viral infection, or by inducing the occurrence of an abnormal immune response.

Aetiology

The pathological changes seen in RE, the occurrence of a preceding infectious or inflammatory event in about 50% of patients, and the similarities with Russian spring-summer tick-borne encephalitis [34] led to the suggestion that the condition was caused by an infection [35], but studies to detect viruses have produced conflicting results. Rasmussen and McCann [36] failed to find inclusion bodies in their pathological specimens, and limited viral studies in five of their patients were negative. Attempts to transmit the disease by intracerebral injections of suspensions of biopsy material in a variety of primates, mice and guinea pigs have been unsuccessful [37]. A search for ten viral antigens with immunoperoxidase stains performed on paraffin-embedded sections from two patients with the condition [38] was similarly negative. However, there have been some positive results. Thus Friedman *et al.* [39] reported virus crystals resembling those of enteroviruses on electronmicroscopy in brain cells from a three year old child with clinical and pathological features of RE, and Walter and Renella [40] identified the Epstein-Barr virus (EBV) genome within the encephalitic infiltrates in two patients. Vinters *et al.* [41] found low levels of EBV and cytomegalovirus (CMV) in the majority of biopsies from children with RE, but also some control biopsies from children without encephalitis: in contrast, Power *et al.* [42] demonstrated CMV genomic material in seven of 10 patients with RE (results that could not be replicated by Farrell *et al.* [43] in three other children), but in only two of 46 control patients with other neurological diseases. McLachlan *et al.* [18], using a CMV DNA probe, were able to show evidence of CMV infection of resected brain tissue from three adults with RE. Jay *et al.* [44] illustrated the difficulty caused by the sensitivity of the various techniques. They tested ten patients with chronic encephalitis and epilepsy, eight patients with encephalitis without epilepsy and five patients with epilepsy but not encephalitis, and were able to demonstrate CMV by polymerase chain reaction (PCR) analysis in 6 of the 10 patients with chronic encephalitis and epilepsy, while in situ hybridization identified CMV in only two, and immunohistochemistry was negative in all cases. Brain biopsy revealed CMV by PCR in two patients with encephalitis but not epilepsy (only one of these was tested by in situ hybridization, and was positive), while PCR in those patients with epilepsy but without encephalitis was negative for CMV (in situ hybridization was not performed in these patients).

The possibility of an immunopathogenetic mechanism underlying RE was suggested by Andrews *et al.* [45], who showed widespread cerebral vasculitis in a hemispherectomy specimen from a young child, with immunofluorescence staining for IgG, IgM, IgA, C3 and C1q, and ultrastructural evidence of vascular injury in addition to severe cortical atrophy with marked neuronal loss (interestingly, another patient with cerebral vasculitis mimicking RE [46] has since been described, while a 7 year old child with clinical and pathological features of RE was reported by Lascelles *et al.* [47] to have developed typical features of systemic lupus erythematosus by the age of 12). However, the direction of research into the aetiology of chronic encephalitis changed abruptly in 1994 when Rogers *et al.* [2] described the development of seizures and histopathological features mimicking RE in two rabbits immunized with GluR3 protein in an effort to raise antibodies to recombinant glutamate receptors (GluRs). This serendipitous finding led them to measure immunoreactivity towards GluR3 and other neural receptors in the serum of four children with RE. Immunoreactivity to GluR3 fusion protein was detected in the sera of two children, one of whom also showed weak immunoreactivity to GluR2 fusion protein, as did the serum from a third child which did not react to other antigens. The serum from the fourth child (who remained seizure-free following a hemispherectomy two years earlier) did not show immunoreactivity to any tested antigen. Sera from controls (four age- and sex-matched children with epilepsy, four without central nervous system (CNS) disease, five with active CNS

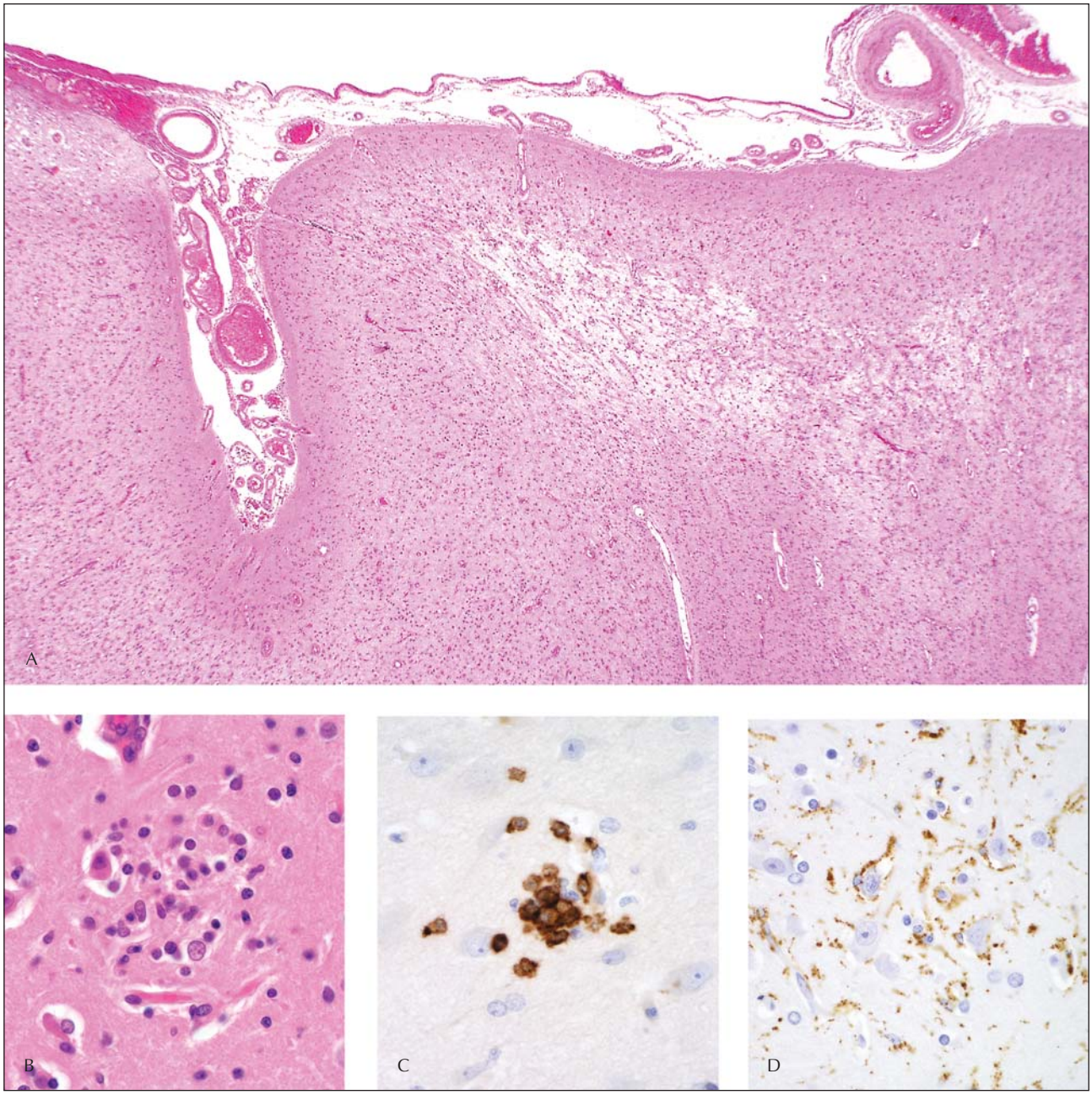

Figure 1. *Pathological hallmarks of Rasmussen's encephalitis.* **A)** *Overview of frontal neocortex with leptomeninges from a hemispherectomy for chronic epilepsy. The cortex is shrunken with widening of the sulci. There is focal spongiosis (light area) alternating with zones of dense astrocytic gliosis.* **(B-D)** *In the active disease process cortical neurons are surrounded by aggregates of inflammatory cells ('microglial nodules')* **(B)** *that contain mainly cytotoxic T-cells* **(C)** *and activated microglia* **(D)** *(positive labelling is indicated by the brown signal). Hematoxylin-eosin* **(A-B)**, *immunocytochemistry for CD8* **(C)** *and CD68* **(D)**. *Original magnifications x40* **(A)** *and x 600* **(B-D).** *(Courtesy Dr Olaf Ansorge).*

disease, four other children with epilepsy, and four normal children) did not show reactivity except for one control serum which showed immunoreactivity to GluR3 different from that seen in individuals with RE. Subsequent plasma exchange in one patient produced a significant improvement in seizure frequency, cognition, and hemiparesis, lending support to the hypothesis that circulating antibodies may contribute to disease pathogenesis, and a further report of three out of four patients (in three of whom GluR3 antibodies had been demonstrated, the fourth not being tested) responding favourably to plasmapheresis soon followed [48]. Further work by Twyman *et al.* [49] showed

that the GluR3 antibodies found in RE activated the glutamate receptors, leading to the hypothesis that the antibodies might directly trigger seizures by overstimulating them. This group and others [3, 50], have suggested that an initial insult to the brain (possibly caused by a systemic infection or a pre-existing pathological lesion, or perhaps even a primary neuronal injury secondary to seizures *per se*) could cause local damage to the blood-brain barrier, permitting access of circulating pathogenic antibodies produced in response to a bacterium (the region of the GluR3 protein with which sera from RE patients reacts being structurally similar to bacterial periplasmic binding domains [51]). Antibody-induced damage could then cause further seizures and the establishment of a "vicious circle" of disease. Although Levite *et al.* [52] showed that in the mouse model, antibodies to the GluR3B peptide bound cultured neurons, evoked GluR ion channel activity, and killed neurons, suggesting that the antibodies were killing neurons by an excitotoxic mechanism (mimicking the effects of excess glutamate), the same group [53] was not able to reproduce the epilepsy seen in RE in GluR3B-immunized mice, even after facilitating the entry of autoreactive antibodies into the brain by weakening the blood-brain barrier, and despite demonstrating pathology resembling that of RE.

Other groups have also emphasised the role of B lymphocytes. In a study to investigate the origin and characteristics of the B cell population that triggers or sustains inflammation in patients with RE, Baranzini *et al.* [54] found substantial perturbations in the normal, unstimulated repertoire of immunoglobulin genes, supporting an important role for clonally expanded B lymphocytes, although they also indicated a wide spectrum of reactivity indicative of antigenic heterogeneity. Whitney *et al.* [55] stained brain samples from patients with RE and controls with complex partial epilepsy for IgG and the C′ factors C4, C8 and the membrane attack complex (MAC). They demonstrated immunoreactivity for IgG, C4 C8, and MAC on discrete patches of cerebrocortical neurons of three patients with RE but not two others, nor the controls. They suggested that activation of the classical C′ pathway by specific, antigen-bound IgG might contribute to the pathogenesis of the disease: the failure to detect such processes in two patients might be explained by a different stage in the disease, sampling error, or differing mechanisms of disease in different patients. They did, nevertheless, note the presence of predominantly $CD8^+$ cells within the parenchyma and in a perivascular distribution, suggesting a possible role for cell-mediated immunity. Others have also suggested that complement-mediated neuronal damage may contribute to the pathology [56].

Despite the initial excitement produced by the report of Rogers *et al.* [2], it rapidly became apparent that this was not the end of the story. Patients were described in whom, despite a beneficial response to immunosuppressive therapy, serum and CSF were negative for antibodies to GluR3 [57], while other authors showed that such antibodies were not specific for RE but could occur in various forms of epilepsy. Thus Wiendl *et al.* [58] tested eight patients with RE, 40 patients with non-inflammatory focal epilepsy, 104 patients with various neurological diseases, and 16 healthy donors, for antibodies against the GluR3 receptor in serum and CSF: the prevalence of GluR3 antibodies was greater in the sera from patients with focal epilepsy than other neurological diseases, but there was no significant difference between patients with RE and those with non-inflammatory focal epilepsy. Mantegazza *et al.* [59] similarly found that anti-GluR3 antibodies were neither specific nor particularly sensitive for RE, but were also present in patients with "catastrophic" epilepsy and intractable seizures.

In recent years, the focus of attention has shifted towards the role of the T-lymphocyte in the pathogenesis of RE [60-66]. Bien *et al.* [62] demonstrated a high density of T cells, microglial nodules and reactive astrocytes (indicating ongoing brain injury), falling with time. In another study [63], they found the inflammatory infiltrates in affected brains to consist mainly of $CD3^+CD8^+$ lymphocytes, with on average, 7.0%, lying in close apposition to neurons. They found the $CD8^+$lymphocytes to stain for Granzyme B (GrB) (a serine protease released by activated cytotoxic T cells into the target cells, where they induce apoptosis), with a polar orientation of the GrB in a vesicular pattern towards the neuron, and postulated a role for cytotoxic T cells at the onset of the disease [64]. They suggested that the neuronal loss so caused, and concomitant release of antigens such as GluR3, might generate secondary, antibody-mediated damage in a subgroup of patients, a hypothesis supported by a study by Gahring *et al.* [65] showing that Granzyme B proteolysis of a neuronal glutamate receptor can generate an autoantigen. Unlike Whitney *et al.* [55], however, they did not find evidence of a role for complement activation on neurons and astrocytes, and suggested that the complement factors might have entered the brain parenchyma non-specifically, for example because of disruption of the blood-brain barrier. Li *et al.* [66] analysed T-cell receptor expression in the brain lesions using PCR, and demonstrated that the local immune response in RE included restricted T-cell populations probably expanding from a few precursor T-cells responding to discrete antigenic epitopes. The same group found a dramatic increase in the expression of several inflammation-related genes, and a striking down-regulation of several GluRs, in particular mGluR4, in a patient with RE with active seizures compared with controls with other neurological or non-neurological conditions, raising the possibility that such changes may play a part in pathogenesis [67]. However, the precise role of T-cell immunity, antibody-mediated mechanisms, and other factors (including viruses) remains to be elucidated.

Electroencephalography

A comprehensive review of the electroencephalographic (EEG) findings in 49 patients with RE seen at the Montreal Neurological Institute between 1950 and 1988 was carried out by So and Gloor [68]. A disturbance of background activity occurs in the vast majority of patients, commonly asymmetrical although usually bilateral. Abnormal slow wave activity, usually polymorphic delta activity, is often present, again usually bilateral with lateralised predominance. Interictal epileptiform discharges occur in most patients, most commonly multiple independent foci lateralised over one hemisphere, with bilateral multiple independent discharges being slightly less common. Bilaterally synchronous, irregular spike and wave or sharp and slow wave discharges are frequent. In the Montreal series, seizures were recorded in 32 patients, the onset being lateralised to one hemisphere in 69%, usually in a multifocal fashion: only five patients had seizures with a strictly localised electrographic onset.

Capovilla *et al.* [69] noted focal delta activity in the left temporal region without spike foci before any MRI changes had developed in a child with RE: they considered that this finding should raise the possibility of the condition in a child developing partial onset seizures in the absence of MRI changes. Andrews *et al.* [70] have suggested a role for EEG in measuring response to therapy after demonstrating a reduction in epileptiform activity and less extension of the epileptic activity beyond the affected hemisphere in patients treated with plasma exchange.

Neuroimaging

The earliest descriptions of the radiological findings (unilateral cerebral atrophy and ventricular dilatation) in children with RE were provided by pneumoencephalography [1]. The arrival of computerised tomography (CT) provided more detail about the changes [71], showing progressive hemiatrophy of varying degree, usually starting in the temporoinsular region, with enlargement of the temporal horn and Sylvian fissure and subsequent spread to involve the rest of the hemisphere. In a few patients, more diffuse cerebral atrophy was seen.

Magnetic resonance imaging shows *(figure 2)*, in addition to these changes, high-intensity signal on proton density and T_2 weighted images in keeping with gliosis [71-73]: one group also noted cerebellar abnormalities [73]. Nakasu *et al.* [74] reported serial MRI changes in a 12 year-old child with RE, who had a normal scan one year after onset of disease, a high intensity lesion in the left frontal

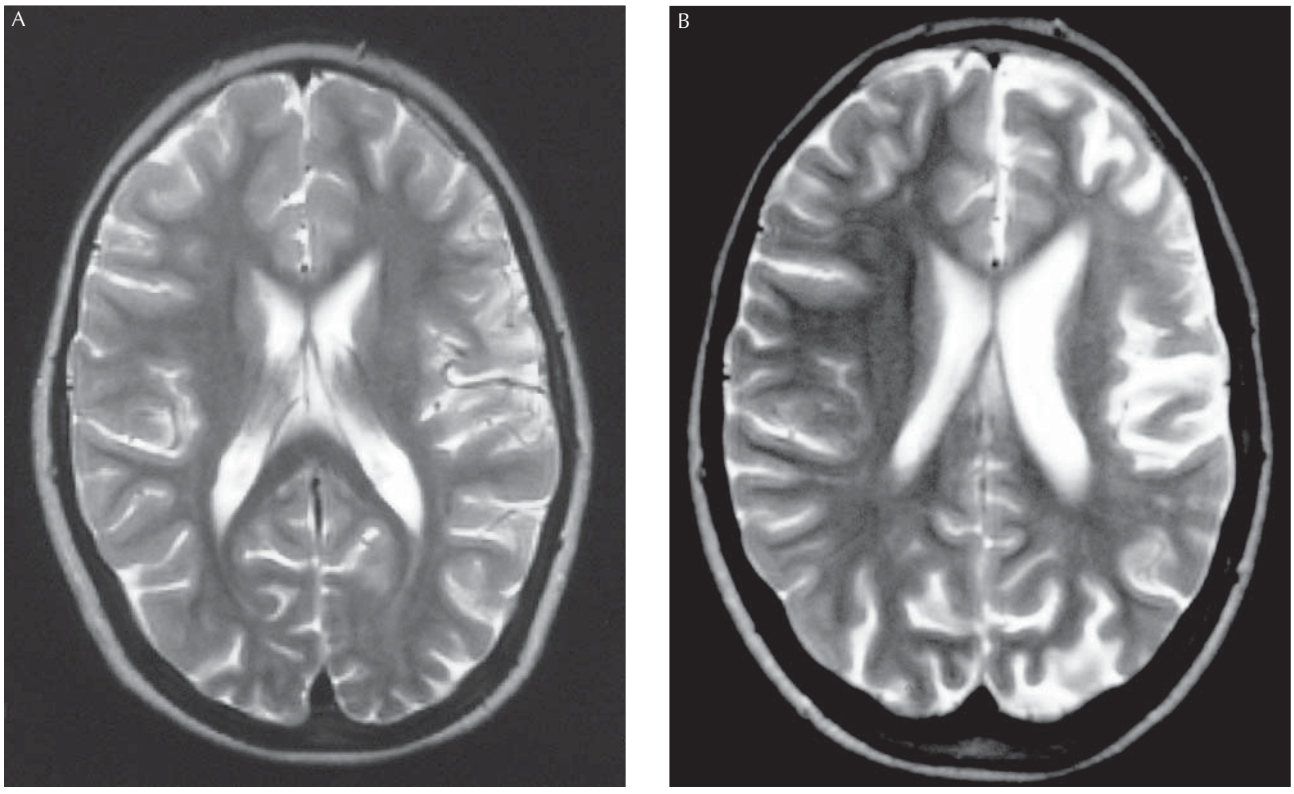

Figure 2. *MRI findings in Rasmussen's encephalitis.* **A)** *"Early Rasmussen's syndrome showing increased signal intensity in the left hemisphere"* **B)** *"MRI from the same patient 4 years later, showing marked atrophy of the left cerebral hemisphere". (Courtesy Dr Philip Anslow)*

cortex in a second scan performed 11 months later, with subsequent spread into the white matter, and regression following biopsy and treatment with intravenous immunoglobulin. A further high intensity lesion developed five months later adjacent to the initial lesion, despite good control of the patient's epilepsy at that time. Two patterns of atrophy have been reported in RE: a relatively uniform, diffuse pattern, and a pattern of focal atrophy superimposed on diffuse atrophy [75].

Bien *et al.* [62] reported a retrospective study of 39 MRI scans in 10 patients with RE treated at the Epilepsy Centre in Bonn between 1990 and 1999. The first change was swelling of the cortex, with a hyperintense T_2/fluid-attenuated inversion recovery signal (stage 1). Later, normal volume and hyperintense signal were seen (stage 2), followed by atrophy and hyperintense signal (stage 3), and then progressive atrophy with normal signal (stage 4). In five patients followed from very early on, the abnormalities were seen to have a focal origin and spread from this across the hemisphere. In three, the first lesion was observed in the temporal lobe (involving the insula in one case), and in two, the first MRI changes were in the frontotemporal regions. Following surgery, an attempt was made to correlate the histopathological changes with the MRI abnormalities: biopsies from stage 2 and 3 areas on MRI were clearly diagnostic for RE, while that from a stage 4 area showed only a few T cells and no microglial nodules. Kim *et al.* [76] carried out a longitudinal study in seven children, and found three patterns of neuroimaging abnormalities: normal MRI followed by increased signal intensity with progressive cortical atrophy over time, initial increased focal signal intensity followed by decrease in spatial extent and degree of intensity, and initially increased signal intensity without further change on follow-up scans.

Magnetic resonance spectroscopy (MRS), which provides an indication of neuronal loss or damage *in vivo,* has shown abnormalities over the entire affected hemisphere [77], including areas that appear normal on conventional MRI, the changes worsening with progression of the disease. Decreased NAA, glutamate, cholines and inositol have also been found in tissue taken from patients with RE [78], the abnormalities varying with the severity and extent of the encephalitis.

Interest has also focussed on functional imaging in RE, using single photon emission computed tomography (SPECT) imaging. A region of hypoperfusion is seen correlating to the presumed area of epileptogenesis as indicated clinically and by EEG [73, 79-81], an increase in cerebral blood flow being shown ictally. Changes in SPECT scanning have also been seen at a time when MRI was normal [82], and may be useful in making the diagnosis. Vinjamuri *et al.* [83] found that the area of hypoperfusion improved in association with clinical response to immunotherapy.

Positron emission tomography (PET) scanning using 18-fluoro-2-deoxy-D-glucose (FDG) shows a regional decrease in metabolism in the affected hemisphere [72, 80]. Banati *et al.* [84] carried out PET using PK11195 (1-[2-chlorophenyl]-N-methyl-N-[1-methyl-propyl]-3-isoquinoline carboxamide) as an *in vivo* marker of activated microglia/brain macrophages, and showed a focal and diffuse increase in binding throughout the affected hemisphere. They suggested that this investigation might help in the choice of appropriate biopsy sites and could also allow assessment of the efficacy of disease-modifying treatment.

Medical treatment

Although the seizures and progressive cognitive impairment can usually be halted by hemispherectomy (*see below*), this is at the expense of hemiparesis if limb weakness has not already developed. Attempts to avoid surgery by trying new medical treatments are therefore ongoing, the choice of treatment largely being dictated by developments in identifying the underlying aetiology.

Treatment of the seizures themselves with antiepileptic drugs has proved disappointing [85], with most patients historically receiving polytherapy causing significant toxicity, and with little effect on seizures. Of the antiviral agents tried, zidovudine was reported as helping one child with RE, neurological deterioration and seizures ceasing for 21 months from the start of treatment, which however had to be stopped after 62 days because of granulocytopenia [86]: Shorvon [personal communication] found zidovudine produced only transient improvement in three patients. Gancyclovir was tried in four patients with RE after cytomegalovirus genome had been found in two (one was not tested) [87]: one child with very frequent seizures became seizure-free within five days of the start of treatment, with improvement in her neurological signs, one patient showed no response, and two, treated 34 and 72 months after the onset of symptoms, showed some improvement. Treatment with intraventricular interferon has also been reported in two patients [88, 89], with some improvement in seizure control in the short term, though in one patient repeated treatments were required.

The recent emphasis in treatment has been on immunomodulatory treatment, particularly steroids, intravenous immunoglobulins, and plasma exchange. The effect of such treatments is difficult to evaluate. RE is rare, and the natural history is for it to "burn itself out" after a variable time, usually after the development of significant neurological deficit. The susceptibility to treatment at different stages of the condition may not be uniform. Practical and ethical considerations would make a placebo-controlled randomised controlled trial difficult, so patients are commonly treated on an individual basis, using variable regimes which, because of the inexorable progression of the

untreated disease, are likely to include several treatments used concurrently or sequentially. Even where patients are treated at a single centre, follow-up may be incomplete.

Steroids have been tried in various centres, often without significant benefit [5, 90]. Dulac *et al.* [91] found short-term improvement following high-dose steroids, with resolution of epilepsia partialis continua in three out of five patients, and improvement in neurological deficit in one, but long-term effects have been more disappointing [27] and at the expense of significant adverse effects. Intravenous immunoglobulin (IVIG) had previously shown encouraging results [92-94] in a few patients with intractable epilepsy. Walsh [95] first reported its effect in RE, in a child of 12 whose illness had developed three years earlier: his symptoms included epilepsia partialis continua and left hemiparesis, both of which improved dramatically with IVIG. The improvement plateaued after six infusions, despite several further infusions being given. After several months, deterioration again occurred, but appeared to respond to further IVIG.

Hart *et al.* [27] reported nineteen patients treated with IVIG and/or high-dose steroids. Nine of these were treated with IVIG, including two being treated concomitantly with steroids. Treatment regimes varied according to the centre, but in most cases IVIG 400 mg/kg/day was given for 3-5 days, commonly followed by a maintenance regime. Seven of the patients, including the two receiving concomitant steroids, showed definite improvement in seizure control. However, in three, this improvement was not maintained despite continuation of the IVIG. A further child showed minor improvement in seizure control and stabilisation of the progress of the disease, but worsened after withdrawal of treatment. One adult patient showed no improvement with IVIG. Whether IVIG ever brings about a prolonged remission in the condition is unclear. However, Wise *et al.* [96] described one girl aged 14 years with typical features of epilepsia partialis continua, secondarily generalised seizures, and mild hemiparesis, who was treated with IVIG, repeated every four months for 46 months, with no progression in motor or cognitive defects during this time, and only rare secondarily generalised seizures. Frucht [14] also described improvement in hemiparesis and cognitive impairment following IVIG, although the patient was treated concomitantly with ganciclovir.

There is some evidence that the response of adults to IVIG may be greater than that in children. Villani *et al.* [97] treated a 45 year-old woman with onset of RE at age 18, who had failed to respond to steroids but who showed an improvement in seizure frequency (including cessation of epilepsia partialis continua) and slight improvement in neurological status following treatment with IVIG. The improvement was maintained for the follow-up period of 10 months. Leach *et al.* [98], reported two patients developing RE in adulthood, both with typical clinical features although in one the histology was non-confirmatory. Anti-GluR3 antibodies were not assayed. Their first patient was treated with IVIG after failure of response to standard antiepileptic drugs, two courses of acyclovir, a right frontoparietal subcortical transection, an attempt at plasma exchange which was abandoned because of thrombosis and infection at the cannulation site, and a brief course of high-dose steroids. The IVIG was given at a dose of 0.4 g/kg body weight per day for five days, repeated every four to six weeks until sustained improvement occurred, then as a maintenance infusion of 0.4 g/kg body weight on one day each month. Clinical improvement, with reduction in seizure frequency and severity and improvement in hemiparesis and intellectual function, were noted after four months of therapy and continued throughout the first year of treatment. The second patient also failed a trial of plasma exchange because of technical problems, and continued to deteriorate despite steroids. IVIG produced a significant improvement in seizure control and hemiparesis, the improvement lasting for the year of follow-up. Cognitive function was also thought to have improved. As a result of this experience, the authors recommended a protocol for adults using these doses, and suggested that the doses previously used in children had been suboptimal. They also found SPECT scanning a useful method of monitoring response.

Little information is available to indicate whether the presence of anti-GluR3 antibodies influences response to treatment. One patient described by Krauss *et al.* [57], in whom GluR3 antibodies were not found, did not respond to IVIG but showed a good response to intravenous methylprednisolone and questionably to cyclophosphamide and plasmapheresis.

Plasma exchange has been effective in some patients but has not usually produced lasting benefit. Following their discovery of GluR3 antibodies in some children with RE, Rogers *et al.* [2] went on to treat one seriously ill, nine year-old girl and brought about improvement in seizure control, cognitive function, speech, and hemiparesis during the first seven weeks. However, over the following four weeks there was again an increase in seizure frequency, with worsening of cognition, speech and motor skills, and increased GluR3 immunoreactivity. Of four patients (three having elevated serum antibodies to GluR3) one (previously described by Rogers) showed initial improvement which was not maintained, one (with GluR3 antibodies) showed no benefit, and one initially responded but developed recurrent central line infections and a deep vein thrombosis. The fourth showed a dramatic response with complete seizure control, recurrence of seizures occurring after two months but again responding to treatment. On the basis of their experience, these authors suggested a protocol involving five to six single volumes of plasma exchange initially, with albumin and saline replacement, spread over 10 to 12 days, with IVIG 1 g/kg being infused immediately after the final plasma exchange and again on

the following day. They recommended subsequent plasma exchange every two to three months as clinically indicated. A another four year-old child with RE [99] in whom methylprednisolone and IVIG were both ineffective showed improvement in seizures and motor activity following plasma exchange, and there was also some lessening of the MRI changes previously present.

Based on the hypothesis that anti-GluR3 antibodies are IgGs, Antozzi *et al.* [100] tested the efficacy of long-term IgG immunoadsorption by protein A (PAI), which selectively removes IgGs from plasma, in a 16 year-old girl who had developed RE at the age of 11, and who was positive for anti-GluR3 IgG antibodies. She showed a dramatic reduction in seizure frequency, and some improvement in hemiparesis: any improvement in cognitive function was limited and patchy. The introduction of monthly infusions of intravenous cyclophosphamide after 15 months failed to help in maintaining the reduced levels of anti-GluR3 antibodies produced by this treatment.

Although these treatments show some promise, none are without adverse effects. Several papers report such complications as infections and thrombosis. Another real risk is that repeated attempts to delay progression of the disease by the use of such treatments may delay definitive surgical treatment beyond the time at which it would have its maximum benefit.

On the basis of the evidence for T-cell involvement in RE, Bien *et al.* [101] treated seven patients in an open trial of tacrolimus, which suppresses the activation of T-lymphocytes. Compared with historical controls, the patients (followed for a median of 22.4 months) had a superior outcome with respect to neurological function and progression of cerebral atrophy, but no better seizure outcome. No treated patient, but seven of 12 control patients, became eligible for hemispherectomy. However, the possibility that the controls had more severe disease from the outset could not be excluded.

Surgical treatment

Despite the advances in medical treatment, none has yet been shown to halt the progress of the disease in the long term. Focal surgical resections have usually been ineffective in controlling seizures [5, 102]. Multiple subpial transection has been used in some patients in whom the predominant area of epileptogenesis was in an eloquent part of the cortex [103, 104]. Hemispherectomy controls seizures in most patients (in the Montreal series, 10 out of 18 patients were seizure-free since discharge from hospital, and six showed major improvement in seizure frequency) [105]. The improvement in seizure control in patients undergoing hemispherectomy may be accompanied by improvement in behaviour and sometimes an improvement in IQ [106]. The late complications of the early procedures, including superficial cerebral haemosiderosis and hydrocephalus, have been largely overcome by the introduction of functional hemispherectomy [107]. Interestingly however, a report of ictal EEG discharges associated with focal hyperperfusion on SPECT within the disconnected hypoperfused hemisphere following functional hemispherectomy [108] suggests that the underlying disease process may continue in the disconnected hemisphere. Although concerns remain about left hemispherectomy in patients developing seizures after early childhood, recent studies suggest that language recovery may occur after left hemispherectomy in children with late-onset seizures [109].

Conclusion

Major advances have been made in recent years in our understanding of the probable factors, particularly autoimmune mechanisms, underlying RE, but at present the precise role played by antibody-mediated mechanisms, T-cell immunity and viral antigens remains unclear. Developments in medical treatment based on these advances are promising, but as yet no treatment has been shown to have a long-term effect sufficient to obviate the need for surgery, and the difficult decision of whether to delay hemispherectomy until hemiparesis has already developed [110], perhaps allowing more time for trials of medical treatment, or to operate early in the hope of preventing intellectual decline [7], will continue to confront us. □

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