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Late-onset Rasmussen's encephalitis and long-term remission

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ABSTRACT – We describe an adult man with biopsy-proven Rasmussen's encephalitis and intractable epilepsy, who underwent excellent recovery. To our knowledge, this is the first report of a patient with Rasmussen's encephalitis who has become completely symptomless, at least for three years, on enhanced antiepileptic and immunological medication.

Key words: late-onset Rasmussen's encephalitis, immunoglobulins

Rasmussen's encephalitis (RE) is a rare chronic inflammatory brain disease. It affects mainly children and leads to a progressive unilateral hemispheric atrophy with profound neurological deficit and intractable seizures (Rasmussen *et al*., 1958; Bien *et al*., 2002; Bien *et al*., 2005). Even though this disease, or similar micronodular encephalitis, is a rarity among adults, the late-onset cases have been increasingly reported (Leach *et al*., 1999; Bien *et al*., 2002; Villani *et al*., 2006; Gambardella *et al*., 2008). Based on these reports, adults may have a more benign and longer clinical course of the disease.

RE usually leads to refractory epilepsy. For the treatment of seizures, hemispherectomy is the preferred choice, at least in advanced disease stages (Bien *et al*., 2005). However, this is not feasible for patients without severe neurological deficits and in these situations other therapeutic approaches have to be considered (Hart *et al*., 1994; Leach *et al*., 1999; Granata *et al*., 2003).

Since the pathogenesis of RE is strongly believed to involve immunological mechanisms (Bien *et al*., 2005), a reasonable therapeutic approach would be to try to prevent the disease progression and drug-resistant seizures by using immunomodulatory or immunosuppressive medications. To date,

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the accumulated knowledge of different immunological treatments, including point of time to start treatment, is sparse, especially in adult patients (Hart *et al*., 1994; Leach *et al*., 1999; Granata *et al*., 2003; Gambardella *et al*., 2008).

We present a 50-year-old man with biopsy-proven RE and intractable epilepsy who was treated with long-term immunomodulation. To date, the patient has been symptomless and seizure-free for three years.

Case report

A previously healthy 41-year-old engineer developed focal motor seizures involving the left hand in April 2001. On neurological examination, no abnormalities were recognised. EEGs were normal during wakefulness and sleep deprivation. Brain MRI showed marginal dilation of the sylvian fissure on the right which was initially considered as normal. Focal epilepsy was diagnosed and the patient was discharged on carbamazepine medication.

Between the years 2001 and 2004, the frequency of seizures varied between one to five per month and most of them occurring after falling asleep. In addition to clonic jerks in the left hand, the patient had left-sided sensomotor seizures affecting both upper and lower limbs with head turning to the left without impairment of consciousness. None of the seizures were generalised. In 2004, the seizures occurred nearly daily. MRI showed no change and ictal video-EEG showed no epileptiform abnormalities, although five stereotypic left-sided motor seizures were recorded. After treatment with a combination of topiramate, clonazepam and carbamazepine, the seizure frequency reduced to the previous level.

In January 2006, after respiratory tract infection, the frequency of focal motor seizures dramatically increased. At this time, the left foot was affected resulting in repeated bouts of epilepsia partialis continua (EPC), which ultimately remained persistent with only a transient response to high-dose intravenous (*i.v.*) fosphenytoin, clobazam and levetiracetam therapy. The ictal video-EEG revealed lateralized epileptic discharges located over the right hemisphere and MRI demonstrated an increased T2 signal in the right gyrus cinguli, in addition to mild atrophy in the right frontal and parietal operculum, identical to the previous MRI *(figure 1)*.

A brain biopsy was obtained. Tissue culture remained negative for *Mycobacterium tuberculosis*, common bacterial species, parasite species and herpes viruses. PCR tests for detecting *Mycoplasma pneumoniae*, *Borrelia burgdorferii*, *Mycobacterium tuberculosis* and polyomavirus, as well as lymphotropic herpes viruses remained negative. There was no microbiological evidence of spongiform disease. Histopathologically, the specimen showed an inflammatory infiltrate with reactive gliosis. Cortical CD68-positive microglial nodules mixed with mainly CD3-positive T-lymphocytes, seen also as perivascular infiltrates, could be observed. Together with clinical features of EPC, this histopathological finding of lymphocytic-microglial encephalitis led to the diagnosis of RE according to the European consensus statement ("B" criteria; Bien *et al*., 2005).

Intravenous immunoglobulin (IVIG) treatment was given at a high dose of 0.4 g/kg body weight per day for five days. After a few weeks, EPC bouts were abolished, and a mild paresis which was recognized in the left food had disappeared. The patient was discharged on a combination of topiramate, levetiracetam and clobazam therapy. Three months later, the signal intensities were remarkably reduced, and in February 2007, totally disappeared.

The patient was seizure-free for 16 months. In July 2007, after respiratory tract infection, he developed EPC involving the left foot. MRI showed new hyperintense T2 signal in the right gyrus cinguli and slight progression of atrophy in a perisylvian area. A second course of high-dose IVIG and fosphenytoin was given with rapid resolution of seizures. Thereafter, a high-dose IVIG course was given monthly.

In October 2007, EPC of the left foot recurred, but was promptly arrested by fosphenytoin loading and *i.v.* methylprednisolone infusion (1 g/d for three days). Oral prednisone therapy (1 mg/kg body weight per day) and phenytoin were added to his medication.

To date, the patient has been seizure-free for three years and his neurological examination is normal. Since autumn 2007, hyperintense signal based on MRI has mainly vanished with no progression of mild right hemiatrophy. In addition to antiepileptic medication, including a combination of carbamazepine, topiramate and clobazam, the patient continues to receive a course of high-dose IVIG (0.7 g/kg body weight per day for one day) monthly.

Discussion

In this case report we describe an adult with biopsy-proven RE and intractable epilepsy who underwent excellent recovery. This case is highly consistent with previous illustrations of this disease in adults (Bien *et al*., 2002; Villani *et al*., 2006). For example, our patient had a long prodromal phase of the disease (five years), consistent with that of earlier adult cases (Hart *et al*., 1997; Leach *et al*., 1999; Villani *et al*., 2006). The other typical feature described in adults is a milder disease course when compared to paediatric patients (Bien *et al*., 2002; Gambardella *et al*., 2008).

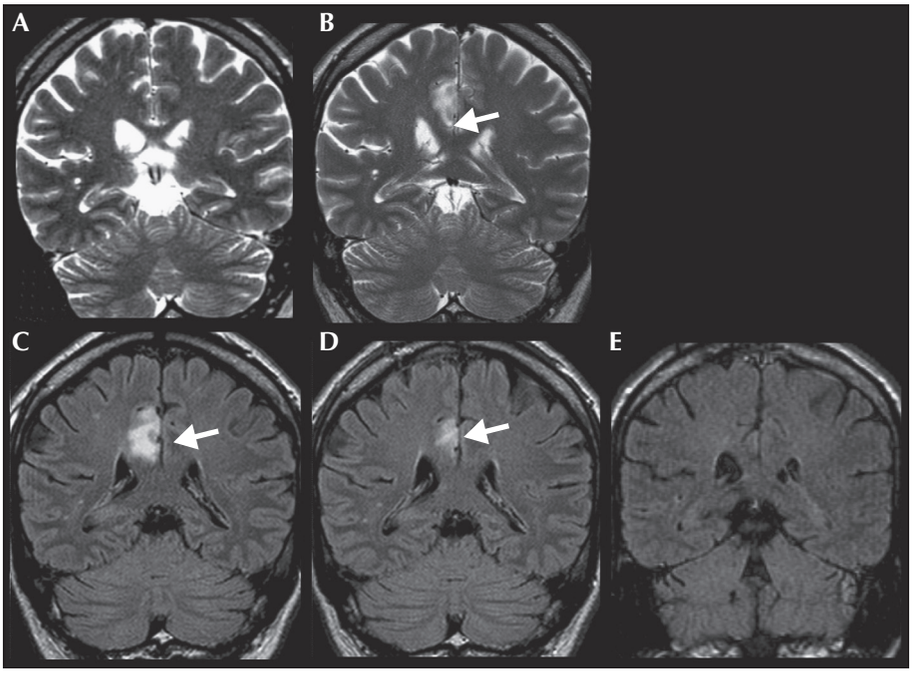

Figure 1. Temporal evolution of the right cingulate gyrus lesion (arrows) shown in coronal T2-weighted (**A**-**B**) or FLAIR (**C**-**E**) images. In 2004 (**A**) the patient was examined due to epilepsy, however, apart from mild cortical atrophy in the right hemisphere, there were no focal abnormalities. In January 2006 (**B**), after worsening of the seizures, an abnormal signal was evident in the lesion. The symptoms progressed and in February 2006 (**C**) the lesion had progressed in size. After biopsy and treatment, in May 2006 (**D**), the lesion had started to show response to therapy. During follow-up, in August 2007 (**E**), the abnormal signal had mainly vanished. The mild hemiatrophy showed no signs of progression by visual analysis.

A more focal and mild form of RE was also seen in our patient who undoubtedly had intractable epilepsy but almost no neurological deficit or cognitive dysfunction.

The most exceptional feature in our case was the patient's good recovery. Having had intractable epilepsy for many years, the patient became totally seizure-free, at least for three years. This kind of seizure freedom is unique even among adult cases and occurs mainly at the last stage of the disease, during which time the patient is profoundly incapacitated with marked brain atrophy (Bien *et al*., 2002; Bien *et al*., 2005); a state which was not present in our patient. Hence, it is assumed that the patient's good recovery was based, at least partly, on therapeutic intervention during and since the acute stage of the disease.

In the acute phase, mild paresis and EPC in the left leg developed. The antiepileptic medication was significantly enhanced and a high-dose IVIG course was given. As a consequence, paresis as well as EPC, gradually vanished. Moreover, other types of seizures, not necessarily related to the inflammatory lesion, were also abolished. This indicates that the enhancement of antiepileptic therapy had a favourable effect on epilepsy in general in this patient. However, we believe that the IVIG treatment was more effective, at least to treat paresis and EPC in the left leg which were clearly caused by inflammation of the right gyrus cinguli; after a first course of IVIG, the EPC and paresis, as well as the inflammatory lesion on MRI, disappeared. Furthermore, EPC bouts did not relapse until the new lesion in the same site was seen.

Previous experience of immunological treatment of RE is based mainly on case reports (Leach *et al*., 1999; Arias *et al*., 2006; Gambardella *et al*., 2008). However, there are two studies consisting of 19 and 15 patients (Hart *et al*., 1994; Granata *et al*., 2003), in which patients were treated with variable combinations of corticosteroids, high-dose IVIG and, in the former study, also with plasmapheresis. In these studies positive time-related responses to seizure frequency and neurological deficit were recognized and indicated that immunotherapy may be considered in the early stages or in more benign variants of the disease, or when surgery is not possible. To date, there is no robust evidence in favour of one treatment over the others, but most often the therapy of choice is IVIG (Bien *et al*.,

2005). IVIG may be beneficial to many patients and has fewer adverse effects than, for example, long-term steroid treatment (*e.g.* fluid retention, osteoporosis or psychosis) (Granata *et al*., 2003; Bien *et al*., 2005).

In the clinical setting, treatment is often guided by the severity and progression of the disease and this was reflected in our management strategy. After the first course of IVIG, the patient was treated only with antiepileptic medication. After the first relapse of EPC, IVIG treatment was repeated every month, and after the second relapse, long-term oral steroid was added to his medication, as recommended by Hart *et al*. (1994). It is unclear whether this drug combination approach was really necessary for this patient and the choice of future treatment following long-term seizure-freedom is furthermore uncertain.

In any case, the patient presented here further contributes to published reports on the clinical presentation of RE-type micronodular encephalitis. The disease progression in adults may be rather limited and the patient may become seizure-free with antiepileptic and immunological medication. In the future, a better therapeutic approach will depend on more available data regarding treatment. As placebo-controlled studies are difficult and even unethical to perform for this disease, the documentation of case reports remains important, not only for patients who achieve good recovery. A better understanding of the efficacy of different treatment strategies in late-onset RE will therefore depend on future studies. □

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References

Arias M, Dapena D, Arias-Rivas S, *et al*. Rasmussen encephalitis in the sixth decade: magnetic resonance image evolution and immunoglobulin response. *Eur Neurol* 2006; 56: 236-9.

Bien CG, Granata T, Antozzi C, *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005; 128: 454-71.

Bien CG, Widman G, Urbach H, *et al*. The natural history of Rasmussen's encephalitis. *Brain* 2002; 125: 1751-9.

Gambardella A, Andermann F, Shorvon S, Le Piane E, Aguglia U. Limited chronic focal encephalitis: another variant of Rasmussen syndrome? *Neurology* 2008; 70: 374-7.

Granata T, Fusco L, Gobbi G, *et al*. Experience with immunomodulatory treatments in Rasmussen's encephalitis. *Neurology* 2003; 61: 1807-10.

Hart YM, Andermann F, Fish DR, *et al*. Chronic encephalitis and epilepsy in adults and adolescents: a variant of Rasmussen's syndrome? *Neurology* 1997; 48: 418-24.

Hart YM, Cortez M, Andermann F, *et al*. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients. *Neurology* 1994; 44: 1030-6.

Leach JP, Chadwick DW, Miles JB, Hart IK. Improvement in adult-onset Rasmussen's encephalitis with long-term immunomodulatory therapy. *Neurology* 1999; 52: 738-42.

Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. *Neurology* 1958; 8: 435-45.

Villani F, Pincherle A, Antozzi C, *et al*. Adult-onset Rasmussen's encephalitis: anatomical-electrographic-clinical features of 7 Italian cases. *Epilepsia* 2006; 47: 41-6.