

Good outcome in adult-onset Rasmussen's encephalitis syndrome: is recovery possible?

Tino Emanuele Poloni¹, Alberto Galli², Anna Pichiecchio³,
Laura di Lodovico⁴, Mauro Ceroni⁴

¹ Service of Neurology, Golgi-Cenci Foundation/ASP Golgi-Redaelli, Milan

² U.O. Neurology, San Carlo Borromeo Hospital, Milan

³ Department of Neuroradiology, IRCCS Istituto Neurologico C. Mondino Foundation, Pavia

⁴ IRCCS Istituto Neurologico C. Mondino Foundation; Department of Neurological Science, University of Pavia, Pavia, Italy

Received September 10, 2014; Accepted February 08, 2015

ABSTRACT – A healthy 29-year-old man suffered from adult-onset epilepsy, characterized by polymorphic progressive seizures resistant to AEDs, leading to unilateral cortical deficits and atrophy of the left hemisphere. The disorder satisfied the clinical, EEG, and imaging criteria for a diagnosis of Rasmussen's encephalitis. During the acute phase of the disease, intrathecal synthesis of specific anti-CMV IgG was identified. This case was characterized by a very mild course and remission of seizures following a treatment with high-dose intravenous polyvalent immunoglobulins containing a high anti-CMV titre. The patient remained symptomless for more than 15 years from clinical onset and more than eight years after the discontinuation of immunological therapy. In agreement with a recent report, this case confirms that adult-onset Rasmussen's encephalitis syndrome may occur with a very mild clinical picture and persistent remission. In this case, the specific index for intrathecal production of anti-CMV antibodies suggested possible CMV involvement, indicating specific immuno-therapy as a treatment choice.

Key words: Rasmussen's encephalitis, focal epilepsy, CMV, immunoglobulins

Correspondence:

Tino Emanuele Poloni
Servizio di Neurologia,
Service of Neurology,
Golgi-Cenci Foundation/ASP
Golgi-Redaelli,
via San Martino n. 10 - 20081
Abbiategrasso,
Milano, Italy
<tepoloni@libero.it>
<e.poloni@golgicenci.it>

Rasmussen's encephalitis (RE) was first described in children as a severe progressive epileptic disorder due to chronic unilateral encephalitis (Rasmussen *et al.*, 1958). More recently, RE has also been reported in adult patients (McLachlan *et al.*, 1993) and, indeed, age at onset is no longer included among the

diagnostic criteria (Bien *et al.*, 2005). Bien *et al.* (2002a) identified three phases of RE: a prodromal phase of variable duration, longer in adults, characterized by focal and secondary generalized seizures without permanent neurological deficit; an acute phase lasting several months with increasing seizures

and spreading encephalitis leading to neurological deterioration and volume loss of the affected hemisphere; and a residual phase characterized by atrophy of the affected hemisphere associated with decreasing seizures and permanent neurological deficit. The outcome of the disease is considered to be generally poor (Varadkar *et al.*, 2014). In the prodromal phase, brain MRI may show swelling and hyperintense T2/FLAIR signal of the affected areas. The acute and residual phases are characterized by signal hyperintensity on MRI, and by progressive hemiatrophy of the brain, accompanied by diminishing inflammation. Contrast enhancement may occur in the prodromal and acute phases (Bien *et al.*, 2002b).

Although RE is associated with an autoimmune aetiology, mainly mediated by T cell cytotoxicity, the primary cause remains elusive and involvement of viral agents has also been proposed (Varadkar *et al.*, 2014). Studies performed using an *in situ* hybridization technique support a possible role of CMV in a number of RE cases (Power *et al.*, 1990; McLachlan *et al.*, 1993). The seizures in RE may improve using immunological therapies. Nevertheless, Rasmussen-like cases may dramatically improve using ganciclovir, a specific anti-CMV agent (McLachlan *et al.*, 2011).

We describe an adult-onset mono-hemispheric encephalitis which fulfils the diagnostic criteria for RE and which was characterized by a very mild course and persistent clinical recovery. Our observation supports the existence of very mild adult-onset RE, as has been recently reported (Kupila *et al.*, 2011).

Case study

A healthy 29-year-old man was referred to us due to the occurrence of clonic jerks in his right hand, three weeks after flu-like symptoms. He had a family history of immunological disorders. Over the following months, he developed a peculiar form of epilepsy with weekly attacks characterized by progressive worsening and spreading of focal seizures including motor, sensory, visual, complex partial, and secondary generalized manifestations. Between the attacks, neurological examination was unremarkable. Brain MRI disclosed several cortical and subcortical foci of hyperintensity on T2-weighted images in the left hemisphere, some of which showed contrast enhancement (*figure 1A*). The EEG showed multi-focal epileptic discharges and persistent slow activity confined to the left hemisphere (*figure 2*). Cranial CT, evoked potentials, and cerebral angiography were normal. Complete screening for auto-antibodies, and for antibodies against *Treponema pallidum*, *Borrelia burgdorferi*, HTLV I, and HIV was negative in blood and CSF. CSF analysis was normal and oligoclonal

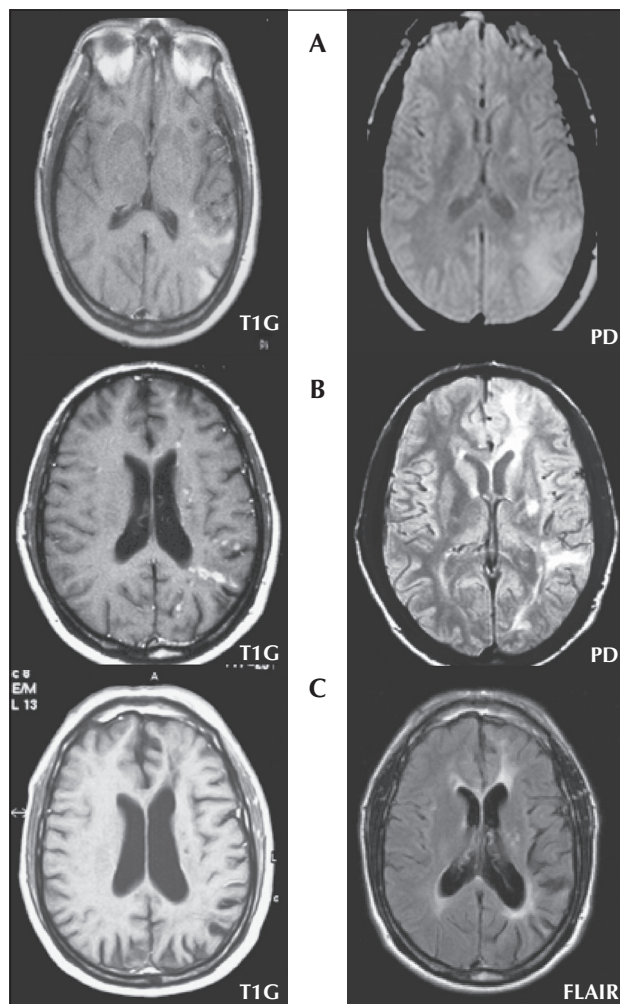


Figure 1. (A) Prodromal phase; MRI showing cortical swelling and hyperintense areas in the left temporal and parietal lobes. Contrast enhancement is clear in the left image. (B) Prodromal/acute phase transition; MRI showing cortical-subcortical hyperintense lesions in the left hemisphere. Contrast enhancement is clear in the left image. An initial atrophy of the left hemisphere is also present. (C) Residual phase; MRI showing left hemispheric atrophy with no contrast enhancement. Atrophy of the head of the left caudate nucleus is also evident. PD: proton density; T1G: T1-weighted gadolinium MRI; FLAIR: fluid-attenuated inversion recovery.

bands were absent. The patient received a steroid course (6-methyl-prednisolone, at 1,000 mg/day for five days, followed by prednisone tapering) and temporarily improved. Subsequently, the disease progressed, leading to several focal and secondary generalized seizures per week. During the following 28 months, he received five courses of steroids to avoid severe evolution of the disease. During each course of steroids, he became seizure-free but then, when on 75 mg/day of prednisone, the epileptic seizures recurred with a frequency of almost one per week. A slight benefit was derived from the combination of valproate

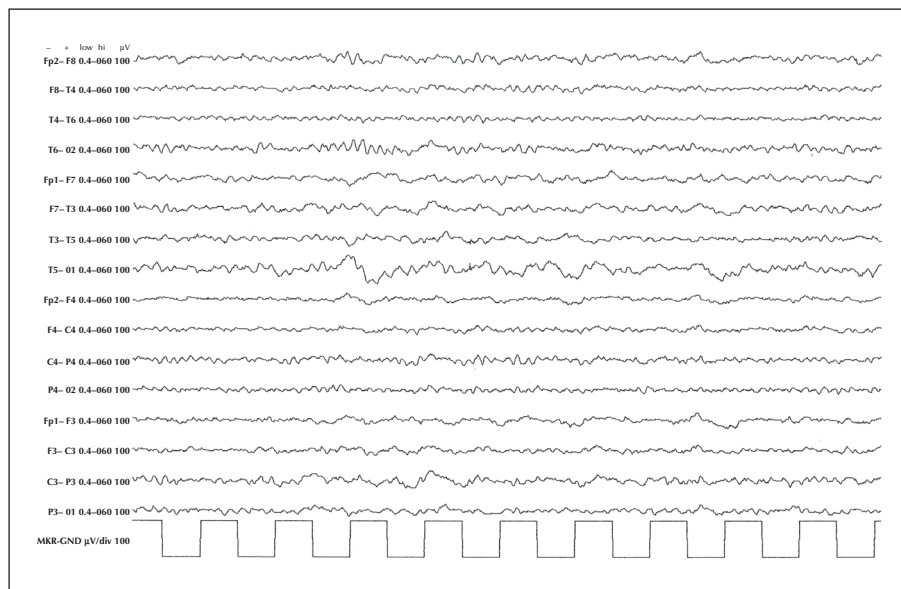


Figure 2. EEG showing slow activity confined to the left hemisphere.

(1,500 mg/day) and carbamazepine (1,200 mg/day), and the patient continued to receive these drugs over the following years.

Three years after the first seizure, the patient developed a progressive mild right hemiparesis with slight aphasic disturbances, mild memory impairment, and depression. The patient underwent further investigations. Repeated brain MRI revealed cortical-subcortical active lesions in the left hemisphere and an evolution towards left hemispheric atrophy. No significant alteration was observed in the right hemisphere (*figure 1B*). Anti-GluR3 antibodies were not found. Antibodies against HSV 1 and 2 and EBV were found only in the serum, whereas anti-CMV IgG was present in both CSF and serum samples; the CSF remained otherwise almost normal. The specific index for intrathecal production of anti-CMV IgG ($[\text{CSF CMV-specific IgG titre/serum CMV-specific IgG titre}]/[\text{CSF albumin concentration/serum albumin concentration}]$) was 5.2 (NV: <1.5), indicating intrathecal synthesis of anti-CMV IgG. A parallel PCR analysis failed to reveal CMV genome in CSF. Such data suggested a previous CMV infection of CNS but no active viral replication. Nevertheless, we started an empirical treatment with high-dose intravenous polyvalent immunoglobulins containing a high anti-CMV titre (HDIV Ig+anti-CMV; Sandoglobulin® with anti-CMV content >50 PEI-U per ml [Novartis Farma, Basel, CH]), a product used to treat CMV infections in immunocompromised subjects. The patient received HDIV Ig+anti-CMV, at 0.4 g/kg/day for five days. After a week, seizure activity was no longer detectable, and he was seizure-free for four months before the next seizure

occurred. During the following four years, the patient received 12 courses of HDIV Ig+anti-CMV (0.4 g/kg/day for three days, every four months). During this period, the patient had only four partial complex seizures. Further MRI (more than 10 years after the onset) confirmed the left hemispheric atrophy, involving the head of the caudate nucleus with no contrast enhancement (*figure 1C*). Considering the good clinical course, the patient refused brain biopsy and it was not performed for ethical reasons. Nevertheless, clinical evolution, EEG, and MRI strongly suggested a diagnosis of RE, according to the European Consensus Statement (Bien *et al.*, 2005). During the following years, the patient remained seizure-free, showing a good functional recovery, and Ig infusions were stopped. In reducing AEDs, rare complex partial seizures recurred and it was decided that the treatment should be maintained. Presently, the patient is seizure-free and able to pursue his normal activities. A recent neurological examination (more than 15 years after the onset) revealed slight right pyramidal signs and a slight loss of discriminative sensation in the right hand, but no major sensory, motor, or neuropsychological deficit.

Discussion

This patient suffered from a chronic, adult-onset, epileptic disorder characterized by polymorphic progressive seizures resistant to AEDs, leading to unilateral cortical deficits (clinical criterion). The EEG showed epileptic discharges and slow activity confined to the left hemisphere (EEG criterion). The MRI

features evolved from a pattern of mono-hemispheric encephalitis to one of left brain hemiatrophy with ipsilateral atrophy of the head of the caudate nucleus (MRI criterion). Thus, the disease and its evolution fully satisfy the clinical, EEG, and imaging criteria for a diagnosis of RE (all three “part A” criteria of Bien *et al.* [2005]). Moreover, the clinical course reflects the prodromal, acute, and residual phases outlined by Bien *et al.* (2002a), and other known conditions, including unihemispheric vasculitis, can be ruled out.

This patient received high-dose steroids and HDIV Ig+anti-CMV during the prodromal and the acute phases; these therapies probably prevented the occurrence of severe brain damage, confirming that immunological treatments are useful, particularly at the beginning of the disease (Bien *et al.*, 2002a, 2002b). Several authors have reported a response to intravenous polyvalent Ig in RE patients, and monoclonal antibodies represent a promising therapeutic approach (Varadkar *et al.*, 2014).

In our patient, CSF analysis indicated a CMV infection of CNS, suggesting possible CMV involvement, and the patient promptly improved after the first course of HDIV Ig+anti-CMV. Although we cannot confirm CMV involvement in our case, the prompt and lasting remission of seizures might also be attributed to the specific activity of anti-CMV Ig. Furthermore, we note that the specific index for intrathecal production of antibodies, which is straightforward to determine, may reveal possible involvement of specific antibodies, which may indicate the use of a particular therapeutic approach. Bien and co-authors classified RE into two groups with different patterns depending upon patient age:

- type 1, developing in childhood and characterized by a more aggressive course; and
- type 2, developing in adolescence and adulthood and characterized by a slower, less aggressive course, with a more protracted prodromal phase.

However, almost all RE reported cases show a severe clinical course (Bien *et al.*, 2002a). The patient reported here had a long prodromal phase, a mild course, and a subsequent clinical recovery. He was followed over a period of more than 15 years. To the best of our knowledge, this is the mildest case of RE reported in the literature with such a long period of clinical observation. Thus, it contributes to broaden the clinical spectrum of adult-onset RE. As underlined in recent reports (Gambardella *et al.*, 2008; Kupila *et al.*, 2011),

very mild RE cases do exist, especially in adulthood, and may have a good outcome, without the need for surgery. As RE is a rare and severe illness, controlled studies are difficult and also unethical, and the report of single cases remains fundamental in order to develop knowledge about this disabling and potentially treatable disease. □

Supplementary Data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

The authors thank Dr Paola Cassini (neurophysiology technician) for the EEG recordings and Mrs. Tere Cassani for her valuable collaboration and help during the preparation of this article. None of the authors have any conflict of interest to disclose.

References

- Bien CG, Widman G, Urbach H, *et al.* The natural history of Rasmussen’s encephalitis. *Brain* 2002a; 125: 1751-9.
- Bien CG, Urbach H, Deckert M, *et al.* Diagnosis and staging of Rasmussen’s encephalitis by serial MRI and histopathology. *Neurology* 2002b; 58: 250-7.
- Bien CG, Granata T, Antozzi C, *et al.* Pathogenesis, diagnosis and treatment of Rasmussen encephalitis. A European consensus statement. *Brain* 2005; 128: 454-71.
- Gambardella A, Andermann F, Shorvon S, *et al.* Limited chronic focal encephalitis: another variant of Rasmussen’s syndrome? *Neurology* 2008; 29: 374-7.
- Kupila L, Jutila L, Immonen A, *et al.* Late-onset Rasmussen’s encephalitis and long-term remission. *Epileptic Disord* 2011; 13: 88-91.
- McLachlan RS, Girvin JP, Blume WT, Reichman H. Rasmussen’s chronic encephalitis in adults. *Arch Neurol* 1993; 50: 269-74.
- McLachlan RS, Diosy D, Levin S. Treatment of Rasmussen’s syndrome with ganciclovir. *Can J Neurol Sci* 2011; 38: 296-8.
- Power C, Poland SD, Blume WT, Girvin JP, Rice GP. Cytomegalovirus and Rasmussen’s encephalitis. *Lancet* 1990; 336: 1282-4.
- Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. *Neurology* 1958; 8: 435-45.
- Varadkar S, Bien CG, Kruse CA, *et al.* Rasmussen’s encephalitis: clinical features, pathobiology, and treatment advances. *Lancet Neurol* 2014; 13: 195-205.

TEST YOURSELF



- (1) Is it mandatory to perform brain biopsy for the diagnosis of Rasmussen's encephalitis (RE)?
- (2) What is the main differential diagnosis of adult-onset RE?
- (3) What are the most important treatments for adult-onset RE?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".