Rasmussen's encephalitis – rare, enigmatic, but instructive

Stephan Rüegg

Why devote an editorial to a very rare disease? Orphan disorders often present the opportunity to decipher basic mechanisms of disease and permit a better understanding of more frequent disorders. This is true for Rasmussen's encephalitis (RE) where epileptologists have become aware of the autoimmune mechanisms influencing or even causing epilepsy, a fact that was initially not obvious at all.

Today, we know that epilepsy in some patients shares an autoimmune origin (such as those with anti-glutamate decarboxylase (GAD) antibodies). On the other hand, epileptic seizures are a main symptom of some autoimmune disorders both systemic (such as systemic lupus erythematodes) and restricted to the central nervous system (as in multiple sclerosis and antibody-mediated [non-]paraneoplastic limbic encephalitis). Interestingly, seizures and epilepsy themselves activate the cellular and humoral immune system which is amongst other things reflected in a postictal increase of pro-inflammatory cytokines or by the presence of inflammatory cells in brain tissue specimens of patients with chronic epilepsy (for review see [1]).

Rasmussen's encephalitis is a very rare, severe epilepsy syndrome most likely of autoimmune origin first reported in 1958 when the neurosurgeon, Theodore Rasmussen, from the Montreal Institute of Neurology presented five children with intractable focal epilepsy, frequent episodes of epilepsia partialis continua and marked contralateral hemispheric atrophy pronounced around the central sulcus. The work of Sheybani et al. in this issue comprehensively summarises the progress in diagnostic means, pathogenetical mechanisms and management of this devastating disorder [2]. Rasmussen himself was struck by the observation of intense perivascular cuffing by „round cells" in the area surrounding very atrophic, scarred brain tissue, and he proposed very localised chronic encephalitis that has smouldered along over a period of years"[3]. This view lasted until 1994 when Rogers et al. reported the discovery of an antibody against glutamate receptors (anti-GluR3), although it was later proved that this antibody was not specific for the disorder [4]. Nevertheless, this prompted others to use plasmapheresis in the treatment of RE with quite some success [5]. The important clinical and histopathological work of Bien and Bauer (summarised in [6]) showed an abundant cytotoxic T-cell-dependent (CD8+-T-LYC) inflammatory process locally destroying brain areas. This type of inflammation points to three possible disease mechanisms: (1) a primary autoimmune process, (2) a secondary autoimmune process triggered by a preceding, most likely, viral infection or (3) a viral infection by a yet undiscovered agent. Extensive search for such a viral origin using large-scale viral genomic testing has failed to detect a culprit (Jan Bauer, personal communication). Open questions remain: What triggers the autoimmune process? Why does it start in the first years of life? Why is the process almost always restricted to one hemisphere? What is the relationship to analogue disorders such as Landau-Kleffner-Syndrome, Continuous Spike-Waves during slow-wave Sleep (CSWS), and Parry-Romberg-Syndrome?

Medical treatment of RE focuses on immunomodulatory compounds as the seizures almost always show complete resistance to all antiepileptic drugs currently available. While immune therapies can often, and in some cases even substantially delay progressive brain destruction, surgical treatment becomes inevitable in the large majority of cases. The surgical intervention consists of removing the scarred and inflamed brain tissue which results in a drastic reduction of seizure activity or even complete freedom from seizures. Although such surgery is performed in functionally very important brain regions, the inflammatory process has already altered these brain structures into a more or less non-functional tissue, thus, the excision does not usually aggravate the functional loss present preoperatively. Technical and computational progress has markedly improved the outcomes of surgery, and increasingly more sophisticated surgical techniques of „hemispherectomies" have reduced the size of the tissue to be sacrificed for the sake of the patients. However, the need to determine the optimal time point for surgery currently remains an important question. To conclude, RE remains a paradigmatic disorder where interdisciplinary teams of epileptologists, neurosurgeons, neuropathologists and immunologists can work together not only to improve patient management and outcome but also to elucidate how epilepsy may be caused and sustained by immune mechanisms.

Correspondence:
Stephan Rüegg, MD
Klinische Neurophysiologie
Neurologische Universitätsklinik
Universitätsspital Basel
Petersgraben 4
CH-4031 Basel
Switzerland
srueegg@uhbs.ch

References

1 Vezzani A, Rüegg S (eds.). Immunity and inflammation in epilepsy: mechanistic insights and therapeutic perspectives. Epilepsia 2011 (Suppl. 3):1–51.
2 Sheybani L, Schaller K, Seeck M. Rasmussen's encephalitis: an update. Schweiz Arch Neurol Psychiatry. 2011;162(6):225–31.
3 Rasmussen T, Olszewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. Neurology. 1958;8:435–45.
4 Rogers SW, Andrews PI, Gahring LC, Whisenend T, Cauley K, Crain B, Hughes TE, Heinemann SF, McNamara JO. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science. 1994;265:648–51.
5 Andrews PI, Dichter MA, Berkovic SF, Newton MR, McNamara JO. Plasmapheresis in Rasmussen's encephalitis. Neurology. 1996;46:242–6.
6 Bauer J, Bien CG. Encephalitis and epilepsy. Semin Immunpathol. 2009; 31:537–44.