Autoimmunity Reviews 15 (2016) 221–225

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmune epilepsy

Antonio Greco [a], Maria Ida Rizzo [a,b], Armando De Virgilio [a,b,*], Michela Conte [a], Andrea Gallo [c], Giuseppe Attanasio [a], Giovanni Ruoppolo [a], Marco de Vincentiis [a]

[a] Department Organs of Sense, ENT Section, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy
[b] Department of Surgical Science, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy
[c] Department of Medico-Surgical Sciences and Biotechnologies, Otorhinolaryngology Section, University of Rome "La Sapienza", Corso della Repubblica, 79, 04100 Latina, LT, Italy

ARTICLE INFO

Article history:
Received 4 November 2015
Accepted 18 November 2015
Available online 25 November 2015

Keywords:
Epilepsy
Autoimmune epilepsy
Autoimmune disease
Refractory epilepsy
Autoimmune seizures

ABSTRACT

Despite the fact that epilepsy is the third most common chronic brain disorder, relatively little is known about the processes leading to the generation of seizures. Accumulating data support an autoimmune basis in patients with antiepileptic drug-resistant seizures. Besides, recent studies show that epilepsy and autoimmune disease frequently co-occur.
Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy.
An autoimmune cause is suspected based on frequent or medically intractable seizures and the presence of at least one neural antibody, inflammatory changes indicated in serum or spinal fluid or on MRI, or a personal or family history of autoimmunity.
It is essential that an autoimmune etiology be considered in the initial differential diagnosis of new onset epilepsy, because early immunotherapy assures an optimal outcome for the patient.

Contents

1. Introduction . . . 221
2. Epidemiology . . . 222
3. Etiopathogenesis . . . 222
4. Symptoms and diagnosis . . . 223
5. Differential diagnosis . . . 223
6. Prognosis . . . 223
7. Treatments. . . . 223
8. Conclusions . . . 223
9. Search strategy . . . 225
Take-home messages . . . 225
References . . . 225

1. Introduction

Epilepsy is a debilitating neurological disorder, characterized by seizures (sporadic electrical storms) and cognitive impairment due to electrical disturbances in the brain, often with neither a known etiology nor an effective treatment.

Accumulating data support an autoimmune basis in patients with antiepileptic drug-resistant seizures. Identification of an immune basis is important because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process in these patients [1–5].

Clinicians caring for patients with either autoimmune disorder or epilepsy should be aware of the strong association between them. A recent population-level study, investigating the relationship between epilepsy and several common autoimmune diseases, examined a total of 2,518,034 individuals (Table 1). It shows that nearly 1 in 5 patients with epilepsy has a coexisting autoimmune disorder [6]. Elevated epilepsy prevalence has been previously reported in autoimmune disorders. Rates of epilepsy in systemic lupus erythematosus vary

* Corresponding author at: Department Organs of Sense, ENT Section, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy. Tel.: +39 380 3408909; fax: +39 06 49976803.
E-mail address: armando.devirgilio@gmail.com (A. De Virgilio).

http://dx.doi.org/10.1016/j.autrev.2015.11.007
1568-9972/

Table 1
Demographic characteristics.
From: Jama Neurol. 2014;71:569–574.

Patients, n	2,518,034
Gender, n (%)	
Female	1,302,709 (51.7)
Male	1,215,325 (48.3)
Age, n (%)	
Children (<18 years old)	476,805 (18.9)
Adults (≤65 years old)	2,041,229 (81.1)
Length of follow-up (days) (mean ± SD)	2571 ± 490
Epilepsy prevalence, n (%)	
All ages	10,041 (0.4)
Children (<18 years old)	1796 (0.4)
Adults (≤65 years old)	8245 (0.4)
Autoimmune disease prevalence, n (%)	
Type 1 diabetes	43,704 (1.7)
Psoriasis	23,542 (0.9)
Rheumatoid arthritis	22,890 (0.9)
Ulcerative colitis	10,690 (0.4)
Hashimoto's thyroiditis	9830 (0.4)
Grave's disease	9758 (0.4)
Systemic lupus erythematosus	9696 (0.4)
Crohn's disease	8774 (0.3)
Antiphospholipid syndrome	5423 (0.2)
Sjögren's Syndrome	3614 (0.1)
Celiac disorder	1885 (0.1)
Myasthenia gravis	1070 (0.04)
Any of the above AD	137,398 (5.5)
Medications[a]	
Aminosalicylates	24,303 (1.0)
Disease-modifying antirheumatic drugs	33,557 (1.3)
Systemic glucocorticoids	790,045 (31.4)
Anti-TNF agents	7114 (0.3)
Other biologics	2915 (0.1)
Non-steroidal anti-inflammatory agents	945,892 (37.6)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.
[a] Excluding medications taken after the first epileptic seizure.

between 4% and 51% and in antiphospholipid syndrome from 3% to 8% [7–11]. A high incidence of seizures also in Hashimoto thyroiditis is reported [12,13].

Autoantibodies have had a recognized role for many years in the genesis of paraneoplastic limbic encephalitis, which frequently has seizures as a prominent feature. Other studies have suggested a role for autoantibodies in epilepsy outside of the bounds of paraneoplastic limbic encephalitis [14]. Indeed, in a cohort study, autoimmune antibodies were detected in 14% of patients with epilepsy [15]. Especially, the role of neural autoantibodies is under investigation in the chronic refractory epilepsy. Besides that, to what extent the damage is caused by the antibodies itself or by the inflammatory reaction in the brain is also debatable.

2. Epidemiology

Epilepsy is a debilitating condition affecting 0.5% to 1.0% of the world's population [6].

It is believed that as many as 10% may be categorized as autoimmune epilepsy, but the real prevalence of autoimmune epilepsy isn't known. The recent findings indicate that the risk of epilepsy is almost four times higher for patients with an autoimmune disease, with 17.5% of epilepsy patients also having an autoimmune disease [1,6]. Seizures tend to occur within the first 1 to 2 years after the autoimmune disorder diagnosis. The risk of epilepsy is consistently higher in children with autoimmune disorder compared with adults with the same autoimmune disorder. Data showed that female sex is associated with a higher risk of epilepsy [7,16–18].

A strong association between incidence of epilepsy and autoimmune diseases is in type 1 diabetes mellitus, psoriasis, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren syndrome, myasthenia gravis, and celiac disease [6].

3. Etiopathogenesis

While brain tumors, trauma or infection can cause epilepsy, the condition can be inherited genetically within families. A growing body of literature demonstrates an autoimmune basis in the etiology of some forms of epilepsy. The link between autoimmune diseases and epilepsy without a recognized neurological cause has been documented for well over a decade [19]. For a long time, such theory lacked an experimental basis. The results of the last years, especially in patients with Rasmussen encephalitis (RE), have given new information about the possible relation between epileptic disorders and the immune system. RE is an autoimmune disorder of the central nervous system, where the serum of the patients contains antibodies to the glutamate receptor GluR3. Immunization of animals with GluR3 induces a disorder resembling the human disease [20–23]. Additional evidence that autoimmune mechanisms operate in RE is in Li's studies, which demonstrated restricted T-lymphocyte populations in the brains of patients with RE. Removal of antibodies by plasma exchange transiently reduces the seizure frequency and improves the neurologic function as the serum concentrations of GluR3 antibodies decrease. As antibodies to GluR3 are found in serum samples from immunized animals without apparent disease, a focal or a general disruption of the blood–brain barrier is essential for serum antibodies to reach the brain [24].

Findings that a substantial number of Rasmussen syndrome patients have increased IgG, CD4 + T cells, TNFα, and Granzyme B in cerebrospinal fluid, suggest that complex pathophysiologic mechanisms involving CD4 + T cells and CD8 + T cells change evolutionally during the progression of Rasmussen syndrome. A crucial cytotoxic process occurs in the early stage, and declines in the progressed stage [25].

The evidence for immunological mechanisms in epilepsy can be examined also in other immunologically mediated diseases. Epilepsy is more common in patients with systemic lupus erythematosus (SLE) who have antiphospholipid antibodies, and it is possible that these antibodies can lead to immune-mediated cortical damage. Between 10% and 20% of patients with SLE develop epileptic seizures at some stage of their disease. This is nearly 8 times the prevalence of epilepsy in the general population. This may mean that long-term treatment with antiepileptic drugs may precipitate SLE, or that epilepsy and SLE occur together as manifestations of a genetically determined predisposition [7–9,16,17].

The recent identification of mutations involving K + channels in benign familial neonatal epilepsy, neuronal nicotinic acetylcholine receptor in autosomal dominant nocturnal frontal lobe epilepsy, and Na + channels in generalized epilepsy with febrile convulsions suggests that autoimmune attack of ion channels could similarly underlie some epileptic disorders. The effects of anticonvulsant drugs, which act on ion channels either to reduce excitatory neurotransmitter release or enhance inhibitory activity, support a role for ion channels in producing epilepsy. In addition, some ion channel drugs (for example 4-aminopyridine, which inhibits K + channels responsible for terminating the nerve action potential and thus prolongs the activation state) may precipitate seizures. Thus, for many reasons ion channels represent good candidate antigens for autoimmune epilepsy and a more widespread and systematic search for anti-ion channel antibodies is indicated [26].

Raised concentrations of serum antibodies, which recognize brain antigens, have been detected in groups of patients with isolated epilepsy [27,28]. A dramatic response to IVIg has been reported in a group of children with refractory seizures [40]. In addition more specific antibodies have been detected in such patients with epilepsy alone [29].

High titers of serum and CSF GABAA receptor antibodies are associated with a severe form of encephalitis with seizures, refractory status epilepticus, or both. The antibodies cause a selective reduction