ELSEVIER

Brain & Development 32 (2010) 51–56

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Epileptic encephalopathy in children possibly related to immune-mediated pathogenesis

Nicola Specchio *, Lucia Fusco, Dianela Claps, Federico Vigevano

Division of Neurology, Bambino Gesù Children's Hospital, IRCCS, P.zza S. Onofrio, 4, 00165 Rome, Italy

Received 8 December 2008; received in revised form 12 June 2009; accepted 9 September 2009

Abstract

Severe epilepsy in the paediatric population negatively influences neurological and cognitive development. Different etiological factors could be responsible of these severe epilepsies, and an early diagnosis could change, in some cases, the neurological and cognitive development. Immune mechanisms have been reported in epilepsy. Epilepsy has been associated with systemic lupus erythematosus, with the presence of anti-phospholipid antibodies (aPL), anti-cardiolipin antibodies, anti-nuclear antibodies, Β2-glycoprotein antibodies, and anti-glutamic acid decarboxylase (anti-GAD) antibodies. CNS inflammation and markers of adaptive immunity have been, also, associated with some epileptic syndromes, such as West syndrome, temporal lobe epilepsy, febrile seizures, tonic–clonic seizures, and tuberous sclerosis. Inflammation and blood–brain barrier (BBB) disruption could be one of the mechanisms responsible for seizure recurrence. Recently clinical entities, characterized by severe epilepsy with a febrile, acute or sub-acute onset, sometimes associated with status epilepticus, followed by drug-resistant, partial epilepsy have been described. Some of these publications also suggested acronyms for the condition described: Acute Encephalitis with Refractory, Repetitive Partial Seizures (AERRPS) reported by Japanese authors, Devastating Epileptic Encephalopathy in School-aged Children (DESC) reported by French authors. Among children with acquired symptomatic severe epilepsy, we identified a group of previously normal children who had developed severe partial epilepsy after an acute/sub-acute illness resembling encephalitis. The etiological factors for those patients seems to remain unknown, and a possible immune-mediating or inflammatory process as pathogenesis of the disease could be hypothesized. More studies need to be addressed to finally define this peculiar epileptic entity.

Keywords: Severe epilepsy; Encephalopathy; Fever; Encephalitis; Immune-mediated; Partial seizures

1. Introduction

Severe epilepsies in the paediatric population negatively influence neurological and cognitive development [1]. This is most evident in patients with normal development prior to the onset of epilepsy, and they could be sustained from different etiological factors. Such clinical entities require careful attention because of the difficulty of a correct diagnosis and treatment, the implication in everyday life, and, moreover in paediatric age, an early etiologic diagnosis could change the neurological and cognitive development. Immune mechanisms are involved in the pathogenesis of some forms of epilepsy; evidence to support this statement has been widely published in the literature [2]. This topic has been investigated in a number of different types of studies that have highlighted epilepsies associated with immune-mediated diseases [3].

In the last years have been reported some groups of patients with epileptic entity characterized by an acute onset of seizures associated with a febrile disease, in previously normal children which resembles an encephalitis,

* Corresponding author. Tel.: +39 06 68592645; fax: +39 06 68592463.
E-mail address: nicola.specchio@opbg.net (N. Specchio).

0387-7604/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2009.09.017

Table 1
Antibodies associated with epilepsy in various diseases.

Antibodies associated with epilepsy
Anti-phospholipid antibodies (aPL)
Anti-cardiolipin antibodies
Anti-nuclear antibodies
Ƀ2-glycoprotein antibodies
Anti-glutamic acid decarboxylase (anti-GAD) antibodies
Anti-voltage-gated calcium channel (VGCC-Ab) antibodies
Anti-voltage-gated potassium channel (VGKC-Ab) antibodies
Antibodies against NMDA receptor

followed by severe epilepsy and cognitive disturbances. Some of these patients could have an immune-mediated disorders as responsible for this peculiar clinical entity.

2. Epilepsy and immunity

Several associations between epilepsy and immunological diseases have been described (Tables 1 and 2). Systemic lupus erythematosus (SLE) and epilepsy have been variably associated (10–20%) [2], and epilepsy has also been associated with the presence of anti-phospholipid antibodies (aPL) [4–6], anti-cardiolipin antibodies [7], anti-nuclear antibodies [8], Ƀ2-glycoprotein antibodies [9], and anti-glutamic acid decarboxylase (anti-GAD) antibodies [10]. Specific serum antibodies have also been associated with a number of CNS diseases. For example, anti-GAD and anti-voltage-gated calcium channel (VGCC) antibodies have been seen in cerebellar ataxia and epilepsy [11], anti-aquaporin-4 antibodies have been associated with neuromyelitis optica [12] and suspected in paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) [13], opsoclonus–myoclonus syndrome, [14,15], and Hashimoto's encephalopathy [16], in which seizures can also occur. In all of these pathologies, the immunological markers are well defined and, consequently, epilepsy is part of the underlying syndrome [11].

Table 2
Epilepsies and Immunological disorders with epilepsy and antibodies.

Disorder	Antibody target
Rasmusseńs encephalitis Drug-resistant focal epilepsy	GluR3
Systemic lupus erythematosus Primary generalised before SLE onset	Phospholipid, Cardiolipin Ƀ2-glycoprotein I
Focal or generalised-tonic during SLE	Antiganglioside antibodies
Therapy-resistant localisation related epilepsy	Cardiolipin, nuclear, Ƀ2-glycoprotein I, anti-GAD
Newly diagnosed seizure	Cardiolipin, nuclear, Ƀ2-glycoprotein I
Generalised epilepsy syndromes West syndrome	Cardiolipin
Cryptogenic Lennox–Gastaut syndrome	Haemocyanin
Epilepsies with good prognosis	Anti-GAD
Hashimoto's encephalopathy	Antithyroid antibodies
Stiff man syndrome (SMS)	Anti-GAD
Cerebellar ataxia and epilepsy	Anti-VGCC

Other insights about the immune-mediated aetiology of some epilepsies come from the detection of AMPA glutamate receptor type 3 (GluR3) in patients with Rasmussen encephalitis [17], and also in other epileptic populations [18]. Laboratory findings suggested the possibility of an immune-mediated component in the pathogenesis of Rasmussen encephalitis [17,19,20]. Additionally, evidence of an immune reaction, such as T lymphocyte infiltration and microglial nodules, has been widely reported [21–23], supporting the use of immuno-modulatory therapies early in the disease course, even though surgical treatment is mandatory in most severe cases [24–26].

3. Epilepsy and inflammation

CNS inflammation and markers of adaptive immunity have been associated with some epileptic syndromes, such as West syndrome, temporal lobe epilepsy, febrile seizures, tonic–clonic seizures, and tuberous sclerosis [27]. Furthermore, it has been hypothesized that chronic epilepsy due to focal cortical dysplasia or other malformations of cortical development could represent, as part of the natural history of epilepsy, inflammatory modifications, which are responsible for acute aggravations of epilepsy [28]. Inflammation and blood–brain barrier (BBB) disruption could be one of the mechanisms responsible for seizure recurrence [29]. It is widely accepted that BBB disruption leads to acute seizures in humans and animal models [30,31]. Loss of BBB function results from inflammatory changes, suggesting a link between seizures, the BBB, and inflammation [29]. An immune-mediated insult could be responsible for BBB disruption, and could subsequently lead to brain edema. Among the phenomena occurring during epileptogenesis in the adult rat brain, inflammation, angiogenesis and changes in BBB permeability properties have recently been described [27]. Inflammation, neovascularization and BBB damage do occur in patients with epilepsy. Experimental studies aimed to investigate the mechanisms regulating angiogenesis and the permeability of the BBB have highlighted that these processes are associated with, and possibly require, the presence of inflammation.

4. Personal data

Among children with acquired symptomatic severe epilepsy, we identified a group of previously normal chil-