Seizures and Epilepsies due to Channelopathies and Neurotransmitter Receptor Dysfunction: A Parallel between Genetic and Immune Aspects

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Abstract
Despite intensive research activity leading to many important discoveries, the pathophysiological mechanisms underlying seizures and epilepsy remain poorly understood. An important number of specific gene defects have been related to various forms of epilepsies, and autoimmunity and epilepsy have been associated for a long time. Certain central nervous system proteins have been involved in epilepsy or acute neurological diseases with seizures either due to underlying gene defects or immune dysfunction. Here, we focus on 2 of them that have been the object of particular attention and in-depth research over the past years: the N-methyl-D-aspartate receptor and the leucin-rich glioma-inactivated protein 1 (LGI1). We also describe illustrative examples of situations in which genetics and immunology meet in the complex pathways that underlie seizures and epilepsy.
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Despite intensive research activity leading to many important discoveries, the pathophysiological mechanisms at the basis of seizures and epilepsy remain incompletely understood.

The role of genetics has long been studied in the field. An important number of specific gene defects have been related to various forms of epilepsies, to the point that the International League against Epilepsy recently proposed a change in terminology by applying the term 'genetic' instead of 'idiopathic' [Berg et al., 2010]. The enormous technological progress made in very recent years has boosted our understanding in the field. With the emphasis and progressive generalization of the use of next-generation sequencing techniques in the diagnostic approach of patients with epilepsy, weeks without important discoveries in the field are rare. Ion channels and neurotransmitter receptors account for a great number of the proteins whose dysfunction has been associated with seizures, and numerous of their encoding genes have been identified. Among many more, these include sodium, potassium or calcium channels, gamma-aminobutyric acid (GABA), or glutamate receptors.

Similarily, autoimmunity and epilepsy have been associated for a long time. Increasing interest started when a group of patients suffering from Rasmussen's encepha-

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litis were found to have circulating anti-GluR3 IgG antibodies in their serum [Rogers et al., 1994], even though later studies showed that this relationship between antibodies against GluR3 peptides and Rasmussen's encephalitis was unclear [Mantegazza et al., 2002]. Up to now, identified antibodies against ion channels mostly target synaptic voltage-dependent channels and ligand-gated receptor channels. Antibodies can be detected in the serum and/or cerebrospinal fluid (CSF) of symptomatic patients. They include voltage-gated potassium channel (VGKC) complex [Lai et al., 2010; Lee et al., 2014], N-methyl-D-aspartate (NMDA) glutamate receptor [Dalmau et al., 2011], gamma-aminobutyric acid A (GABA$_A$) and B (GABA$_B$) receptors [Kruer et al., 2014; Petit-Pedrol et al., 2014], glycine receptor [Carvajal-González et al., 2014], dipeptidyl-peptidase-like protein-6 (a subunit of the Kv4.2 potassium channel) [Boronat et al., 2013], metabotropic glutamate receptor 5 [Lancaster et al., 2011], and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) [Joubert et al., 2015]. During the past years, knowledge on autoantibodies and associated neuropsychiatric manifestations including epilepsy has skyrocketed.

Interestingly, certain of the above-mentioned central nervous system (CNS) proteins have been involved in epilepsy or acute neurological diseases with seizures either due to underlying gene defects or immune dysfunction. Here, we focus on 2 of them that have been the object of particular attention and in-depth research over the past years: the NMDA receptor and the leucin-rich glioma-inactivated protein 1 (LGI1) related to the VGKC complex. We also describe illustrative examples of situations in which genetics and immunology meet in the complex pathways that underlie seizures and epilepsy.

Part 1: NMDA Glutamate Receptors

NMDA receptors are ligand-gated ion channels composed of 2 glycine-binding NR1 and 2 glutamate-binding NR2 subunits. These receptors are widely distributed in all regions of the CNS and carry important functions in brain development and cognition [Endele et al., 2010; Aida et al., 2012; Turner et al., 2015a, b]. Well-delineated, but nevertheless very different clinical pictures have been linked with mutations in the genes that encode subunits of the receptor and with circulating autoantibodies targeting one of these subunits. The following paragraphs briefly describe these entities.

Epilepsy and Seizures Linked to Mutations in NMDA Receptor Genes
GRIN2A
Abnormalities in *GRIN2A*, the gene that encodes NR2A, the alpha-2 subunit of the NMDA receptor, have been recently reported in patients with idiopathic focal epilepsies with rolandic spikes, including benign epilepsy with centrotemporal spikes (BECTS), Landau-Kleffner syndrome, and epileptic encephalopathy with continuous spike-waves during slow sleep (CSWS) [Carvill et al., 2013; Lemke et al., 2013; Lesca et al., 2013; Conroy et al., 2014; Turner et al., 2015a, b].

In one of the 3 seminal papers published simultaneously in 2013 on that topic, new heterozygous mutations were discovered in 27 (7.5%) of 359 affected individuals from 2 independent cohorts with idiopathic focal epilepsies. Twelve (4.9%) of 245 patients with BECTS and 9 (17.6%) of 51 patients with CSWS had mutations, indicating a possible correlation between phenotype severity and an increased risk of carrying a mutation [Lemke et al., 2013]. In that article, functional analysis of a missense mutation found in one of the patients suggested increased activation of the NR1-NR2 heteromer, contrasting with data resulting from previous studies on other types of mutations affecting the same gene [Lemke et al., 2013].

In a second article, *GRIN2A* deletions and point mutations were detected in 20% of familial and sporadic cases of Landau-Kleffner syndrome, CSWS, and atypical rolandic epilepsy often associated with speech disorders [Lesca et al., 2013].

In the third article, in a total of 519 patients with epileptic encephalopathies, 4 (9%) of 44 patients with epilepsy-aphasia syndromes had pathogenic *GRIN2A* mutations. These 4 patients all belonged to families in which several members were diagnosed with conditions in the same epilepsy-aphasia syndromes spectrum. In that cohort, *GRIN2A* mutations were neither identified in any of the other encephalopathies, nor in patients with BECTS [Carvill et al., 2013].

This last finding was later confirmed in another study on a large group of patients with either generalized epilepsy or so-called 'temporal lobe epilepsy', in which none of several hundreds of patients with these conditions had mutations in *GRIN2A* [Lal et al., 2015].

Additional variable phenotypes have been associated with *GRIN2A* in patients with seizures [Endele et al., 2010]. Further studies are necessary to better understand the protein function and genotype-phenotype associations.

GRIN2B

Mutations in *GRIN2B*, the gene encoding NR2B, the beta-2 subunit of the NMDA receptor, have been reported in patients with intellectual disability [Endele et al., 2010] and various neuropsychiatric conditions, such as disruptive behavior [Lee et al., 2016], autism [Pan et al., 2015], and Tourette syndrome [Che et al., 2015]. However, epilepsy does not seem to be predominant in most conditions related to *GRIN2B* product dysfunction [Endele et al., 2010]. In a large cohort of 264 children with West syndrome or Lennox-Gastaut syndrome screened by exome sequencing, only one was identified as carrying a de novo mutation in *GRIN2B* [Epi4K Consortium et al., 2013]. To our knowledge, only rare additional patients with West syndrome or focal seizures (all in the context of developmental delay/intellectual disability) and *GRIN2B* mutations have been reported since [Lemke et al., 2014].

NMDA Receptors as Antigenic Targets of Circulating Autoantibodies

Circulating antibodies against glutamatergic NMDA-receptor (NMDAR) subunits have been reported in association with various forms of encephalitis and seizures. Animal studies showed that antibodies mainly react against the extracellular N-terminal domain of the NR1 subunit of the NMDAR [Dalmau et al., 2008]. The presence of anti-NMDAR antibodies has been shown to provoke an increase in the NMDAR internalization rate in hippocampal neurons, subsequent decrease in NMDAR-mediated currents, and a decrease in inhibitory synapse density onto excitatory hippocampal neurons [Hughes et al., 2010; Moscato et al., 2014]. Brain biopsies performed in rare patients show mild perivascular lymphocytic cuffing, microglial activation, or normal findings [Dalmau et al., 2008].

In the initial cases reported, these antibodies were considered as nonspecific markers of an ongoing autoimmune process. Later, however, these antibodies were clearly identified as being directly responsible for a homogeneous association of neuropsychiatric symptoms observed in many patients [Dalmau et al., 2007, 2008]. The patients present with a characteristic sequence of behavioral or cognitive changes of subacute appearance (days to weeks) followed by transient seizures. In the series published in 2008, 76% of patients had seizures in the first 3 weeks of the disease. These were of various types, including focal motor or dyscognitive, generalized tonic-clonic, and refractory status epilepticus or epilepsia partialis continua [Dalmau et al., 2008]. Focal (mostly tonic)

seizures with a suggestive ictal-onset pattern (rhythmic and sharp 6–12 Hz activity with a subsequent spread to one or both hemispheres) have also been reported in children [Sands et al., 2015]. A severe movement disorder, including orofacial dyskinesias, dystonia, and choreoathetosis, is subsequently observed. Central hypoventilation, sleep disturbances (in form of hyper- or hyposomnia), and autonomic dysfunction may be noted as well. This quite homogeneous clinical presentation was individualized as 'anti-NMDAR encephalitis' in the groundbreaking article of 2008 [Dalmau et al., 2008]. It has been shown since that anti-NMDAR antibodies are one of the most frequent causes of encephalitis in children and young adults, all infectious and inflammatory etiologies included, as demonstrated recently in a large cohort study [Gable et al., 2012].

Since 2008, multiple patients have been reported, including children whose presentation closely resembles that of adults, although dysautonomia and respiratory troubles may be more frequent or severe in the latter [Florance et al., 2009]. One report of a transplacental transfer of NMDAR antibodies in a child who was later diagnosed with abnormal neonatal movements, developmental delay, seizures, and cortical dysplasia has been published recently [Jagota et al., 2014]. The question whether all or part of this child's clinical symptoms and findings result from the transfer of maternal antibodies remains unanswered.

NMDAR antibodies are frequently found in the CSF of patients. Additional findings in that compartment may include an elevated cellular (mostly lymphocytic) and protein count as well as oligoclonal distribution. Three distinct clinical-radiological syndromes involving the white matter were recently identified in children with anti-NMDAR encephalitis [Hacohen et al., 2014]. Some of these patients had associated antibodies involved in demyelination, such as those targeting myelin oligodendrocyte glycoprotein. In many patients, structural MRI remains normal. FDG-PET scan studies have shown variable sites of involvement in a few patients, such as hypermetabolism in the basal ganglia and cortical hypometabolism in a patient with prominent abnormal movements, and hypermetabolism in the left prefrontal and anterior cingulate cortex in another patient with psychiatric features and seizures [Maeder-Ingvar et al., 2011; Chanson et al., 2012]. Functional imaging studies recently showed reduced functional connectivity of both hippocampi and extensive white matter changes on diffusion tensor imaging sequences, most prominent in the cingulate cortex [Finke et al., 2013]. The EEG most often shows

Table 1. Comparison between epilepsy related to NMDAR autoantibodies and to *GRIN2A* mutations

	Autoimmune	Genetic
Etiology	unknown, alleged predisposition to autoimmune diseases	mutation in *GRIN2A*
Age of onset	mostly young adults, rarely children, female predominance	childhood
Symptom development	subacute onset, long course (months) and possible recurrence, seizures often transient at disease onset	subacute/acute onset of clinical features including acquired auditory aphasia related to sleep EEG abnormalities, rare seizures in most cases
Ictal presentation	focal motor or dyscognitive seizures, generalized seizures, status epilepticus, epilepsia partialis continua	focal motor seizures in most cases
Interictal presentation	behavioral troubles, cognitive difficulties	asymptomatic or acquired aphasia, loss of speech, behavioral troubles
Other findings	movement disorder, sleep difficulties, autonomic dysfunction	none reported
EEG	focal or diffuse continuous theta and delta slowing, superimposed low-voltage fast activity (extreme delta brush pattern)	biphasic stereotyped centrotemporal spike-waves, may become continuous during sleep, especially if cognitive decline is noted
Brain MRI	frequently normal, may show white matter abnormalities	normal
Treatment	refractory to AED, recover with immunotherapy and extended intensive care support	seizures AED responsive, EEG abnormalities often refractory
Outcome	appropriate treatment started early, complete recovery is the rule; cognitive or motor sequeleae may be observed, rare deaths reported	cognitive sequeleae often observed

a slow background activity with monotonous features that suggest a predominant involvement of subcortical structures. All of the EEGs performed on the patients reported in 2008 were abnormal: of 92 patients for whom information was available, 71 had slowing and 21 had epileptic activity [Dalmau et al., 2008]. Low-voltage fast rhythms may be superimposed on slow waves, creating the so-called and easily recognizable 'extreme delta-brush' pattern [Schmitt et al., 2012; Armangue et al., 2013].

The disorder may be associated with tumors, frequently located in the ovaries in young women. This association seems much less common in children [Florance et al., 2009]. Symptoms are typically refractory to all neuro- and psychoactive drugs but most often respond well to immunotherapy and tumor removal [Titulaer et al.,

2013]. Immune treatment recommendations include the aggressive use of steroids, plasma exchanges, and immunoglobulins as first-line approaches, rapidly followed by monoclonal antibodies (rituximab) and cyclophosphamide in case of refractoriness [Dalmau et al., 2008; Florance et al., 2009; Titulaer et al., 2013]. Complete disappearance of symptoms can be expected, but recovery may take up to 18 months; a minority of patients may die during their illness [Titulaer et al., 2013].

The main clinical differences between epilepsy related to *GRIN2A* mutations and anti-NMDAR encephalitis are described in table 1. Since both entities share different pathophysiological mechanisms, it is not surprising that clinical presentation differs between them. Another main difference lies in the treatment response. Autoimmune-

mediated epilepsy is a potentially reversible episodic phenomenon by means of immunomodulatory treatment, while genetically determined disorders may persist due to an absence of causal therapy.

Part 2: Voltage-Gated Potassium Channel Complex/ LGI1

LGI1 is a protein linked to the VGKC complex and whose mutations or autoimmune pathology may cause epilepsy. The discovery of LGI1 has raised great interest in epilepsy research since it was the first epilepsy-related gene appearing to code for a protein and not for an ion channel. Only later studies identified its close relationship with the VGKC complex [Irani et al., 2010]. LGI1 was then shown to be the major target of human autoantibodies which immunoprecipitate VGKC complexes from mammalian brain tissue, while contactin-associated protein-like 2 (CASPR2) is the second antigenic neuronal target.

LGI1 belongs to large synaptic protein complexes linked to VGKC and is associated with the disintegrin and metalloprotease domain-containing proteins (ADAM)-22 and ADAM23. By binding to ADAM22 and ADAM23, LGI1 also acts on AMPAR, which are glutamate receptors and cation channels at the postsynaptic membrane. LGI1 is also complexed with Kv1.1-containing presynaptic VGKC and prevents its fast inactivation, possibly via interaction between ADAM23 and the intracellular Kvβ1 subunit [Fukata et al., 2010; Crisp et al., 2016]. In total, LGI1 participates in a trans-synaptic protein complex that includes presynaptic potassium channels and postsynaptic AMPAR.

Besides LGI1, mutations in other potassium channels have been involved in other epileptic syndromes: *KCNQ2* and *KCNQ3* are genes whose mutations cause familial benign neonatal convulsions [Singh et al., 2003] as well as early-onset epileptic encephalopathies [Weckhuysen et al., 2012]. To our knowledge, there are no known mutations inducing epilepsy in the *KCNA1* gene encoding the Kv1.1 channel (on which LGI1 acts), except in mice models [Robbins and Tempel, 2012], but *KCNA1* mutations cause another paroxysmal neurological disorder – episodic ataxia type 1 [Graves et al., 2014].

Autosomal Dominant Partial Epilepsy with Auditory Features/LGI1 mutations

The *LGI1* gene, also called epitempin, is located in chromosome 10q22 and encodes a protein (LGI1) which was first found to have a tumor suppressor function. Mis-

sense or truncating mutations as well as microdeletions were shown to be involved in a rare form of lateral temporal lobe epilepsy with auditory auras, known as autosomal dominant partial epilepsy with auditory features (ADPEAF), autosomal dominant epilepsy with auditory features [Gu et al., 2002; Klein et al., 2013], or autosomal dominant lateral temporal lobe epilepsy [Pisano et al., 2005]. Diagnosis of ADPEAF is fulfilled whenever 2 or more family members experience auditory auras or sensory aphasic seizures [Ottman, 2007].

The prevalence of this affection is currently unknown, with dozens of families reported, particularly in Italy [Michelucci et al., 2013]. The age of onset is variable ranging from 8 to 50 years [Michelucci et al., 2003] but usually emerging in adolescence and early childhood [Ho et al., 2012]. Clinical presentation is characterized by simple auditory auras such as ringing, humming and mainly buzzing with a progressive increased intensity (>50%), sometimes followed by a secondary generalization (66%) [Michelucci et al., 2013]. More complex auditory symptoms have been described but remain an infrequent clinical complaint. Seizures with prominent auditory auras are sometimes triggered by external noises [Michelucci et al., 2003; Pisano et al., 2005]. Language ictal disturbances (i.e., aphasia) have also been reported as a frequent clinical feature [Michelucci et al., 2003]. Autonomic manifestations, classically observed in mesial temporal lobe epilepsy, were not described in 8 families suffering from ADPEAF of European ancestry [Ottman et al., 2004]. Less frequently, other types of auras such as visual, motor, dyscognitive, and even vertigo have been reported [Dazzo et al., 2015; Klein et al., 2016].

Interictal EEG shows rhythmic epileptiform temporal abnormalities such as focal slowing or sharp waves in up to 2/3 of individuals with a slightly left predominance [Brodtkorb et al., 2002]. EEG was reported as normal or showing nonspecific changes in about one third of the patients [Michelucci et al., 2013]. Structural MRI is sought to be unremarkable; however, subtle focal abnormalities such as temporal lobe enlargement or atrophy have been rarely described [Kobayashi et al., 2003; Tessa et al., 2007].

Approximately 40 *LGI1* mutations accounting for ~50% of the affected families have been reported in the literature so far [Michelucci et al., 2003; Ottman et al., 2004]. These mutations preferentially involve the N-terminal leucine-rich repeat (LRR) responsible for protein-protein interface. An average penetrance of 66% has been reported, but selection bias is suspected since they are based on families selected for the study containing a large number of affected individuals [Rosanoff and Ottman,

2008]. Clinical differences could partly be explained by the presence of diverse types of mutations in the *LGI1* gene. A recent study by Ho et al. [2012] tried to establish a genotype-phenotype correlation by showing that families with few auditory auras had truncation mutations in the epitempin domain (exons 7, 8) instead of the LRR region (exons 1–6). This would mean that even though mutations in the epitempin and the LRR domain are clearly pathogenic, LRR is more frequently associated with 'typical forms' of ADPEAF.

As opposed to ADPEAF, sporadic cases seldom present with *LGI1* de novo gene mutations (around 2%) [Bisulli et al., 2004; Nobile et al., 2009; Kesim et al., 2015]. This finding was confirmed by a study comparing a group of 16 patients with a sporadic form of idiopathic partial epilepsy with auditory features versus European families with a known *LGI1* mutation [Flex et al., 2005]. Clinical presentation, disease evolution, and response to antiepileptic drugs (AED) are sought to be the same in both groups [Bisulli et al., 2004].

Notwithstanding the genetic evidence underlying ADPEAF, the pathogenic mechanisms leading from an *LGI1* mutation to focal epilepsy remain elusive. It has been hypothesized that LGI1 deficiency triggers epilepsy as a result of a faulty interaction with the proteins ADAM22 and 23, which affects AMPAR-mediated synaptic transmission [Fukata et al., 2010]. More recently, it was shown that LGI1 depletion in glutamatergic pyramidal neurons applied in conditional knockout mice generates seizures per se, at any moment of the neural development, independently if it occurs in the prenatal (i.e., mimicking familial ADPEAF) or the postnatal period [Boillot et al., 2014]. The defect was only patent when it affected glutamatergic neurons and not GABAergic neurons. In addition, further evidence suggests that mutant LGI1 inhibits dendritic and synaptic pruning of glutamatergic neurons during the postnatal period and thus markedly increases excitatory synaptic transmission in transgenic mice expressing a truncated mutant form found in ADPEAF [Zhou et al., 2009]. Alternatively, another hypothesis involved the fact that LGI1 could prevent the fast inactivation of presynaptic VGKC Kv1.1 [Schulte et al., 2006], possibly by an interaction between ADAM23 and the intracellular Kvβ1 subunit [Crisp et al., 2016]. Moreover, recent evidence suggests that LGI1 deficiency results in a presynaptic dysfunction leading to an increased glutamatergic synaptic transmission [Yu et al., 2010; Boillot et al., 2016]. In summary, all *LGI1* mutations induce a loss of function of the protein (haploinsufficiency), whether by a loss of expression (1/3 of the mutations), or an absence of secretion or absence of interaction with its main receptor, ADAM22.

New light has been shed regarding the genetic heterogeneity of ADPEAF; a recent Italian-American study has identified 7 heterozygote missense mutations in the *RELN* gene in 7 families with ADPEAF showing no *LGI1* mutations [Dazzo et al., 2015]. *RELN* encodes REELIN, a glycoprotein regulating neuronal migration [Hong et al., 2000], which does not seem to interfere with channels.

Limbic Encephalitis Associated with Anti-LGI1 Antibodies

VGKC-related autoimmune disorder includes distinct clinical syndromes ranging from pure peripheral to exclusive CNS involvement. At one extreme, acquired neuromyotonia, or Isaacs' syndrome, presents with peripheral motor nerve hyperexcitability [Vincent, 2010]. At the other end of the scale, limbic encephalitis (LE) is defined by its exclusive CNS involvement and characterized by psychosis, cognitive disturbances, sleep disorder, myoclonus, and seizures of acute or subacute onset [Pollak et al., 2014; Crisp et al., 2016]. Unlike some forms of neuromyotonia, only ~10% of VGKC-related LEs are associated with tumors, whether from lung, thyroid, kidney, ovary, or thymus [Irani et al., 2010; Lai et al., 2010] and are, thus, potentially reversible in ~90% of patients receiving immunosuppression [Tan et al., 2008]. Supportive criteria comprise personal or familial history of other autoimmune diseases, pleocytosis in CSF, and nonspecific white matter changes depicted on MRI [Ekizoglu et al., 2014], whereas exclusion criteria include other causes such as infectious, metabolic, or toxic. In addition, oligoclonal distribution, considered as a confirmative element of a CNS autoimmune process, can be detected in ~50–60% of all patients at one stage of the disease.

Phenotypic heterogeneity of VGKC-related disorders can be explained by the fact that autoantibodies are directed towards other neural proteins that coprecipitate with Kv1.1 subunits, but not to the complex itself [Lai et al., 2010; Vincent and Irani, 2010]. A recent scientific breakthrough has shown that autoimmune LE, previously attributed to VGKC-complex antibodies, is mostly due to autoantibodies targeting LGI1 [Lai et al., 2010]. LGI1 and CASPR2 have been identified as the major targets of potassium channel antibodies [Irani et al., 2010; Klein et al., 2013].

LE associated with anti-LGI1 antibodies mainly affects patients in their seventh decade (mean age: 60 years; range: 30–80 years) with a slight male predominance [Lai et al., 2010]. Subacute and progressive altered conscious-

ness, prominent amnesic features (100%), drop attacks (62%), and faciobrachial dystonic seizures (FBDS) (82–90%) associated with temporal lobe EEG discharges characterize LE associated with LGI1 antibodies [Andrade et al., 2011; Irani et al., 2011]. Besides the constantly observed memory loss and the frequent epileptic focal seizures, myoclonia (present in 40% of all cases) and hyponatremia (60% of all cases, with a mean level of 128 mmol/l) are frequently encountered [Lai et al., 2010].

Stereotypic, brief (<3 seconds) and unilateral facial grimacing (76%) and dystonic posturing of the ipsilateral upper limb, appearing several times a day, constitute the hallmark of FBDS [Lai et al., 2010]. This clinical manifestation can appear from one to several months before the onset of cognitive disturbances [Irani et al., 2011]. FBDS seems to be related with LGI1 antibodies, since no FBDS was reported in 5 Korean patients with CASPR2 antibodies [Sunwoo et al., 2015]. Even though ictal and peri-ictal dysautonomic features such as tachychardia, blood pressure abnormalities, or hypersalivation are primarily observed in anti-NMDAR encephalitis (see above, Part 1) or Caspr2 encephalitis [Baysal-Kirac et al., 2016], pilomotor seizures [Rocamora et al., 2014] and bradycardia [Naasan et al., 2014] were respectively described in 3/5 and in 3/14 patients in association with LGI1 antibodies.

Interictal EEG shows a continuous theta and delta diffuse slowing in about 75% of the patients with autoimmune LE [Baysal-Kirac et al., 2015]. Ictal abnormalities showed a frontotemporal, frontal or temporal focus [Irani et al., 2011].

Brain MRI depicted an increased T2/FLAIR signal involving one or both mesial temporal lobe(s) in 43/57 patients with LGI1-mediated LE in the acute/subacute phase [Lai et al., 2010]. In addition, a voxel-based morphometry study showed a gray matter volume increase in both amygdalas in LGI1-mediated LE as opposed to anti-glutamic acid decarboxylase-associated LE [Wagner et al., 2015]. A 3-year follow-up study showed global brain atrophy with hippocampal sclerosis in one patient who did not receive immunosuppressive therapy [Szots et al., 2014].

CSF analysis is abnormal in about 40% of the patients with either elevated protein or lymphocytic pleocytosis [Lai et al., 2010].

The epileptic seizures respond more favorably to immunosuppression than to AED, often showing cutaneous side effects ranging from a local rash to Stevens-Johnson syndrome in AED-treated patients [Irani et al., 2011]; on the other hand, an early immunotherapy may prevent the appearance of cognitive impairment [Irani et al., 2013].

Falls in serum of VGKC antibodies were correlated with an improvement in neuropsychological tests in 6/10 patients [Vincent et al., 2004]. Moreover, recovery time was highly correlated with the speed of treatment onset. The faster the treatment was introduced, the more rapid the clinical recovery was achieved. Steroids and intravenous immunoglobulins have been the more frequently administered treatments, whereas plasma exchanges are more rarely used. The outcome is a full recovery of all symptoms in a quarter of the patients, mild disability in 54%, moderate disability in 16%, and death in 6% in the study of Lai [Lai et al., 2010].

Understanding the pathogenic mechanisms of this disease is of utmost importance in treatment decision-making. Most likely, different autoimmune synaptic encephalopathies carry diverse antibody-mediated mechanisms. One hypothesis elaborated by Ohkawa et al. [2013] suggests that binding of antibodies to LGI1 disrupts the ligand-receptor interaction of LGI1 with ADAM 22. The latter interacts with postsynaptic density protein 95 (PSD-95), also known as DLG4, thus leading to a reduction in the amount of AMPARs in the synapses. A different mechanism but a similar result (i.e., decrease in AMPARs) is observed in AMPAR-related LE, explaining why similar clinical presentations are observed in both cases, despite the strong association with an underlying tumor in the latter [Höftberger et al., 2015]. Interestingly, AMPARs mediate fast excitatory as well as long-term potentiation of synaptic transmission in the CNS, which are mechanisms implicated in memory consolidation [Granger et al., 2013], a feature that is disturbed in both AMPAR and LGI1-mediated LE. Increased intrinsic hyperexcitability could be responsible for ictal manifestations [Peng et al., 2015]. Despite the fact that LGI1 antibodies are mainly an IgG4 subclass of IgG, strong evidence points out complement-mediated mechanisms as a plausible cause of hippocampal injury [Bien and Bauer, 2014]. No matter which of these hypotheses is considered valid, these changes at a molecular level can be translated as a synaptic function reduction of VGKC containing LGI1 (irreversible effect of the antibodies on the VGKC-related antigens) and, thus, increased excitability, as shown by a work on rat hippocampal slices after administration of VGKC antibodies from a patient [Lalic et al., 2011].

The small sample size and uncontrolled nature of most studies constitute a major limitation in assessing treatment efficacy. To our knowledge, no controlled, randomized trial has been performed showing superiority of a particular first-line therapy: plasma exchange,

Table 2. Comparison between epilepsy related to LGI1 autoantibodies and to *LGI1* mutations

	Autoimmune	Genetic
Etiology	unknown, alleged predisposition to autoimmune diseases	mutation in *LGI1* (chromosome 10q22)
Age of onset	adult: 30–80 years (median 60 years), male predominance	childhood/adolescence
Symptom development	brutal onset, monophasic course	lifetime condition, no disease progression
Ictal presentation	FBDS; status epilepticus; mesial temporal seizures without auditory features; autonomic dysfunction such as bradycardia, hypersalivation, and piloerection; drop attacks	focal seizure with auditory auras (simple or complex) and secondary generalization; other sensory, motor, and dyscognitive auras rarely reported; no reported autonomic manifestations
Interictal presentation	psychosis; memory loss	asymptomatic
Other findings	hyponatremia	none reported
EEG	continuous theta and delta slowing, temporal or frontotemporal lobe discharges	interictal epileptiform temporal abnormalities such as focal slowing or sharp waves with a slightly left predominance, 1/3 showed normal EEG or nonspecific abnormalities
Brain MRI	increased T2/FLAIR signal involving one or both mesial temporal lobe during acute phase, global brain atrophy and hippocampal sclerosis >3 years after disease onset	normal or minor abnormalities such as temporal lobe malformation, temporal arachnoidal cysts, mild ventricular asymmetry, white matter gliotic changes, or mild hippocampal atrophy
Treatment	refractory to AED, recover with immunotherapy and extended intensive care support	AED responsive
Outcome	dependent on treatment onset, possible cognitive deficits	benign

intravenous immunoglobulin, or pulse intravenous methylprednisolone. Second-line therapy such as rituximab, cyclophosphamide or both has not been applied in LE associated with LGI1 antibodies so far; however, treatment association resulted in favorable clinical outcome in patients with VGKC-complex LE [Wong et al., 2010]. In a recent review by Bien and Bauer [2014], the potential use of eculizumab as an attractive therapeutic option has been tackled, given its encouraging results in other complement-mediated CNS disorders such as neuromyelitis optica spectrum disorder. In any case, early recognition of LE and intractable seizures or status epilepticus as possible features of autoimmune synaptic encephalopathy would allow for prompt introduction of immunotherapy in order to treat the epileptic seizures and prevent future cognitive disturbances, such as epi-sodic memory and verbal fluency disturbances, and long-term brain MRI changes [Irani et al., 2011; Szots et al., 2014].

Thus, it appears that either genetic or acquired loss of the LGI1-ADAM22 interaction will reduce the function of the AMPAR and favor seizures and epilepsy [Ohkawa et al., 2013]. The main clinical differences between epilepsy related to *LGI1* mutations and encephalitis associated with anti-LGI1 antibodies are described in table 2.

Part 3: The Relation between Immunity and Genetics

Autoimmune disorders are defined by the expression of autoantibodies causing antibody- or cell-mediated damage, possibly in genetically susceptible individuals

and in the presence of predisposing environmental factors [Picascia et al., 2015]. A strong association between seizures and autoimmune diseases is indubitable. In a recent population-level study, Ong et al. [2014] showed that the risk of having epilepsy was more important in patients with one of the 12 common systemic autoimmune diseases studied, as compared to control subjects without such conditions. The overall relative risk of epilepsy was 3.8 times higher in adults, and 5.2 times higher in children with any of these conditions. Patients with autoimmune diseases collectively accounted for 17.5% of all patients with epilepsy of the entire population [Ong et al., 2014]. Inherited gene defects and somatic mutations allowing a higher affinity for infectious microorganisms could 'accidentally' trigger autoimmune disease, resulting in a ruthless growth of self-reactive B and T lymphocyte 'forbidden clones' leading to intrathecal or intraparenchymal antibody production [Adams and Knight, 2003].

The concept of autoimmune epilepsy has recently arisen. Specific signaling cascades of the innate immune system, activated by various 'external' stimuli (such as stroke, trauma, etc.), have been hypothesized as playing a major role in immune predisposition leading to epilepsy. These include the production of interleukin-1 beta (IL-1β) by activated astrocytes and microglial cells, leading to increased neuronal excitability and increased secretion of high mobility group box 1 from necrotic cells, interacting with Toll-like receptor 4 (TLR-4, a pathogen recognition receptor and mediator of inflammation response) to activate neuroglial gene transcription of factors involved in inflammation, astrocyte dysfunction, neurogenesis, and sprouting [Matin et al., 2015]. Additional inflammation factors, such as IL-8 and ATF-3, have also been related to epilepsy, but gene expression studies on human tissue from pharmacoresistant patients with temporal lobe epilepsy seem to indicate that the concentration of these factors is inversely correlated with seizure frequency [Pernhorst et al., 2013].

In any case, these mechanisms remain poorly known [Bien and Bauer, 2014]. It is still unclear why certain patients with seizures show signs of CNS or systemic immune system involvement and whether these mechanisms are at the basis of or appear in reaction to seizures is unknown. It is nevertheless tempting to hypothesize the existence of a possible direct link between genetic predisposition to immune system dysfunction in certain forms of seizures and epilepsies. The following illustrative examples may bring new insights to our understanding of the question.

Febrile Seizures

Febrile seizures (FS) are the most common form of seizures observed in the general population. They concern 2–5% of affected children, mostly aged between 6 months and 5 years [Stafstrom, 2002]. A recent multicentric prospective study evaluated long-term consequences of febrile status epilepticus on 200 children and showed MRI (hippocampal and temporal lobe) [Shinnar et al., 2012] and EEG abnormalities (1/3 presented focal temporal slowing) [Nordli et al., 2012] within the first 72 h, while CSF analysis was unremarkable [Frank et al., 2012].

Family history of febrile seizures is frequently positive, suggesting underlying genetic predisposition for an abnormal response to fever. Among others, mutations in genes coding for sodium channels or GABA receptors were identified in certain families with FS [Greenberg and Holmes, 2002]. Additional data, in particular from twin studies, indicate that inheritance is probably heterogeneous and polygenic, and that environmental factors are likely to be important in the pathogenesis of FS. Inflammatory response components, such as those involved in the interleukin 1 (IL-1) system, have been suspected to play a role in FS [Gatti et al., 2002]. Recent reports indicate that certain SNPs in genes that encode other inflammation-related molecules, such as IL-6 [Shahrokhi et al., 2014], IL-6 receptor, prostaglandin E receptor 3, purinergic receptor P2X7, or TLR-4, may be involved in the pathogenesis of FS [Emsley et al., 2014].

Post-Traumatic Epilepsy

The expression and concentration profile of IL-1β, a proinflammatory cytokine, was recently studied in patients with post-traumatic epilepsy [Diamond et al., 2014]. IL-1β is produced in the CNS by activated microglia and astrocytes, and in the blood mostly by macrophages; it was previously demonstrated to be increasingly expressed and chronically released after traumatic brain injury, and hence, to contribute to the appearance of subsequent post-traumatic epilepsy in certain patients [Ferrari et al., 1996; Lu et al., 2005; Diamond et al., 2014]. A specific SNP in *IL-1B*, the gene that encodes IL-1β, had itself been involved in certain forms of nontraumatic temporal lobe epilepsy in other studies [Kauffman et al., 2008]. Based on these data, the aim of the study by Diamond et al. [2014] was to determine if genetic variability within *IL-1B* and if specific IL-1β profiles contribute to post-traumatic epilepsy. Indeed, in a group of 59 adults with traumatic brain injury and available acute cytokine information, higher CSF/serum Il-1β ratios were associated with an increased risk for post-traumatic epilepsy.

Interestingly, genetic analyses showed a significant relationship between a heterozygous CT genotype in a specific SNP (rs 1143634) and increased risk of post-traumatic epilepsy, shorter time to first seizure, lower serum IL-1β levels, higher CSF/serum ratio as well as increased *IL-1β* gene expression compared to CC or TT homozygous patients [Diamond et al., 2014]. The authors hypothesize that these findings reflect a genetic variability of the function of the blood-brain barrier after traumatic brain injury in certain individuals, which would allow proinflammatory cytokines to penetrate the CNS and cause permanent damage.

Epilepsy in Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a rare neurocutaneous disease associated with mutations in *TSC1* and *TSC2*, 2 tumor suppressor genes whose products (hamartin and tuberin, respectively) are involved in downregulation of the mammalian target of rapamycin complex 1 (mTORC1) [Saxena and Sampson, 2015]. Clinical symptoms are due to loss of function of these proteins leading to overactivation of mTORC1 signaling [Aronica and Crino, 2014]. This pathway modulates different cell development stages ranging from neuronal maturation to death and shares histopathological similarities to other focal malformations of cortical development [Lim and Crino, 2013].

Clinically, TSC is characterized by the development of hamartomatous lesions in various body organs, such as tubers in the CNS. The spectrum of clinical manifestations is large. Seizures occur in 75–90% of all patients [Thiele, 2004] and may present as epileptic spasms during the first year of life or as focal seizures related to cortical tubers. Refractory epilepsy may develop, and certain patients require surgical management to control seizures.

The pathophysiological mechanisms that underlie seizures in these patients are currently unknown. Inflammatory markers have been noted in cortical tubers or peri-tuberal tissue [Boer et al., 2008a] and have long been suspected to play a role in seizure genesis in that disorder. Various research teams have studied the expression of certain genes in cortical tubers resected from patients who underwent epilepsy surgery. In addition to abnormal expression of genes encoding GABA$_A$ receptor subunits and glutamate receptors [White et al., 2001; Boer et al., 2008b; Talos et al., 2008], also observed in other forms of drug-resistant epilepsy, the expression of genes associated with the immune system and the inflammatory response, such as those encoding cell adhesion molecules, complement factors, serpin A3, chemokine ligand 2 and

several cytokines, was also shown to be increased in tubers, compared to control tissues [Boer et al., 2010]. This phenomenon was particularly noted in tubers where the mTOR cascade is highly activated, suggesting a direct effect of the latter on that specific gene activation [Boer et al., 2010]. In addition, several proinflammatory cytokines such as TNF-α and IL-1β might intervene on the expression and disintegration of neurotransmitter receptors, thus, producing a stimulation or response blockage.

Conclusion

Certain channelopathies and dysfunctional neurotransmitter receptors are illustrative examples of well-studied conditions causing neurological manifestations such as seizures via different mechanisms. These mechanisms include gene defects as well as immune system alterations. Important differences exist in the way these symptoms are expressed in both situations, even in the case of a same channel/receptor involvement. Why this is the case remains to be fully understood. Likewise, whether certain individuals carry a genetic predisposition to abnormal immune reactions related to seizures is currently unknown. Further studies in the field are of utmost importance to improve our current state of knowledge, which may open up interesting therapeutic approaches for patients with channelopathy-related seizures and epilepsy.

Disclosure Statement

The authors declare no conflicts of interest.

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