Immunomodulation in Adult Epilepsy: The Role of IVIG

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ABSTRACT: Much of the research for intravenous immunoglobulins (IVIG) use in epilepsy has focused on childhood epilepsies and the results have been inconclusive. As evidence for inflammation in epilepsy and epileptogenesis is accumulating, IVIG might have a role to play in adult epilepsy. Our literature review focuses on the purported mechanisms of IVIG, the link between inflammation and the various causes of adult epilepsy and the different steps of epileptogenesis at which inflammation might play a role. We also review the current clinical evidence supporting IVIG as a treatment for epilepsy in the adult population. Though there is interesting theoretical potential for treatment of refractory epilepsy in adults with IVIG, insufficient evidence exists to support its standard use. The question remains if IVIG should still be considered as an end-of-the-line option for patients with epilepsy poorly responsive to all other treatments.

RÉSUMÉ: Immunomodulation dans l'épilepsie chez l'adulte : le rôle des IVIG. La recherche sur l'administration intraveineuse d'immunoglobulines (IVIG) dans l'épilepsie a porté surtout sur les épilepsies de l'enfance et les résultats ne sont pas concluants. Étant donné qu'il existe de plus en plus de données sur l'inflammation dans l'épilepsie et l'épileptogenèse, l'IVIG pourrait également avoir un rôle à jouer dans l'épilepsie chez l'adulte. Notre revue de littérature visait les mécanismes putatifs de l'IVIG, le lien entre l'inflammation et les différentes causes de l'épilepsie chez l'adulte et les différentes étapes de l'épileptogenèse au cours desquelles l'inflammation pourrait jouer un rôle. Nous revoyons également les données cliniques actuelles en faveur de l'IVIG comme traitement de l'épilepsie dans la population adulte. Bien qu'il existe un potentiel théorique intéressant en faveur de ce traitement de l'épilepsie réfractaire au traitement chez les adultes, les données disponibles n'appuient pas son utilisation courante. On ne sait toujours pas si l'IVIG devrait encore être considérée comme une option de dernier recours chez les patients dont l'épilepsie répond mal à tous les autres traitements.

One of the oldest uses of intravenous immunoglobulins (IVIG) is for treatment of epilepsy. Possible benefit from IVIG for seizures was first observed as early as 1977 when children who received IVIG for treatment of their recurrent upper respiratory tract infections also experienced significant control of their chronic seizures[1]. Though the evidence supporting a role for the immune system in epilepsy continues to accumulate, it has not yet resulted in sufficient enthusiastic support for immunomodulatory treatments, such as IVIG, to be considered standard treatment.

The bulk of the literature pertaining to IVIG as a treatment for epilepsy has focused on childhood epilepsies. Depending on the exact target of IVIG in epileptogenesis, IVIG might have a role to play in adult epilepsy as well. However, it is important to clearly identify the population of interest for IVIG, given that its hefty cost and non-negligible side effect profile (anaphylaxis in IgA deficiency[2], thrombosis[3], acute renal failure[4], aseptic meningitis and other neurological complications[5,6]) will likely prohibit it from ever reaching the ranks of first-line therapies for otherwise well-controlled epilepsy. Of particular interest is the potential for use of IVIG as a treatment for refractory epilepsy and status epilepticus, conditions that carry a significant risk for

the patient and a high burden for the health care system. Despite a vast array of anti-epileptic drugs available to the adult patient, approximately 36% of patients do not achieve seizure control after three drug trials[7]. Status epilepticus (SE) is also a condition very relevant to the adult neurologist as it occurs relatively frequently in the elderly (>60 years-of-age) with an incidence of 86 per 100,000 per year, second only to the incidence in infants[8]. The associated mortality has been found to range from 2 to 40% depending on the population studied and, again, is highest in the elderly[9]. These numbers help highlight the need for additional treatments for refractory epilepsy and status epilepticus in vulnerable patient groups. Intravenous immunoglobulins has

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recently emerged as a treatment option in such cases, and has been recommended as part of the treatment algorithm for refractory status epilepticus, even in the absence of a clear immunologic cause[10,11].

The goal of this paper is to examine the theoretical and clinical evidence for IVIG use in adult epilepsy. The literature will be reviewed regarding (1) the purported mechanisms of IVIG as a treatment for epilepsy, (2) the link between inflammation and different seizure etiologies in the adult population, (3) the experimental evidence supporting a role for inflammation in epileptogenesis, and (4) the clinical evidence supporting IVIG use in epilepsy with particular attention to literature pertaining to the adult population. We acknowledge that other immunomodulatory treatments, such as steroids and plasma exchange, are occasionally used for refractory epilepsy. However, in this review we chose to focus on IVIG given its accessibility and the fact that of these other therapies, IVIG has already received the greatest attention.

MECHANISM OF ACTION OF IVIG

Intravenous immunoglobulins is a natural purified blood product pooled from over 1000 human blood donors. It is composed mainly of immunoglobulin G (IgG) (95%) and the remainder is IgA with negligible concentrations of IgM[12,13]. It has multiple mechanisms of action, though no single mode has been identified as the crucial mechanism. The mechanisms can be broadly categorized into immunomodulatory and neuro-modulating effects.

The immune system is broadly composed of innate and adaptive immune responses. The innate immune response is the non-specific immediate response that provides defense against any type of pathogen (non-self antigen). It relies on inflammatory cytokines to induce recruitment of immune cells and on the complement cascade and antibody-complex formation for clearance of pathogens. The adaptive immune response is then engaged by antigen-presenting cells and

provides the ability to recognize and remember non-self antigens by mounting cell-mediated and humoural responses[14]. IVIG interferes with both responses[13,15]. These effects are summarized in Table 1.

Intravenous immunoglobulins may also have neuro-modulating effects and studies in rats have suggested a direct anticonvulsant effect, probably through actions on the immune system, by either increasing levels of neuroprotective cytokines such as IL-6 or decreasing production of cytokines that may potentiate seizures[16-18].

Of utmost importance for the treatment of epilepsy is the certainty that IVIG can cross the blood-brain barrier (BBB). It has been shown that IgG easily enters the CSF and can be measured by a two-fold increase in IgG concentration (compared to the five-fold increase measured in the serum) after a full dose of IVIG in patients treated for autoimmune neuromuscular conditions[5,13,19]. In addition, it is thought that seizures increase BBB permeability, possibly owing to increases in cerebral blood flow[20] or to the local effect of seizure activity[21], which might further enhance passage of immunoglobulins across the BBB. That IVIG reaches the central nervous system (CNS) supports the possibility that local suppression of inflammation and direct neuromodulating effects might be relevant mechanisms for seizure control.

THE ROLE OF IVIG IN ADULT EPILEPSY: TARGETING THE UNDERLYING ETIOLOGY

Guidelines published by the National Advisory Committee on Blood and Blood products (NAC) and Canadian Blood Services have recommended the use of IVIG for 14 neurological conditions, all of which have a clear immune-mediated pathogenesis, but did not include epilepsy. Intravenous immunoglobulins was not recommended for intractable childhood epilepsy and was not evaluated for adult epilepsy or status epilepticus[22]. Given that the main effect of IVIG is immunomodulatory, an important question to ask to clarify the role of IVIG in adult epilepsy is: What step in epileptogenesis is immune-mediated (Figure)? This is a challenging question and the answer, at least in part, depends on the underlying seizure etiology, of which there are many.

In adults with newly diagnosed epilepsy, the etiology is most often structural or metabolic. Common causes include: pre- and peri-natal insults, cerebrovascular disease, traumatic brain injury, congenital malformations such as cortical dysplasias and vascular lesions, CNS infections, brain tumors, and limbic encephalitis[23-25]. In the elderly, cerebrovascular, degenerative and neoplastic causes are more common than in younger adults[26,27]. Of these causes, a few, such as congenital malformations[28,29], cerebrovascular disease[30], head injury[31] and degenerative diseases[32,33], have more recently been postulated to have an immune basis, while others, such as temporal lobe epilepsy and autoimmune encephalitis, have been demonstrated to have a clearer link with the immune system. We will focus on the latter.

Temporal lobe epilepsy

The presence of an inflammatory response in mesial temporal lobe epilepsy (MTLE) has been the focus of much attention recently with the observation that resected brain tissue from

Table 1: Summary of immunomodulatory effects of IVIG

| Primary effect	Secondary effect
Suppresses pathogenic pro-inflammatory cytokines	Decreases levels of circulating interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and IL-1β
Interferes with complement uptake	Prevents formation of macrophage attack complexes
Blocks Fc receptor on macrophages	Interferes with antibody-dependent cytotoxicity
Inhibits phagocytosis of antigen presenting cells	Prevents activation of innate immune response
Supplies anti-idiotypic antibodies	Neutralizes autoantibodies and prevents interaction with autoantigens
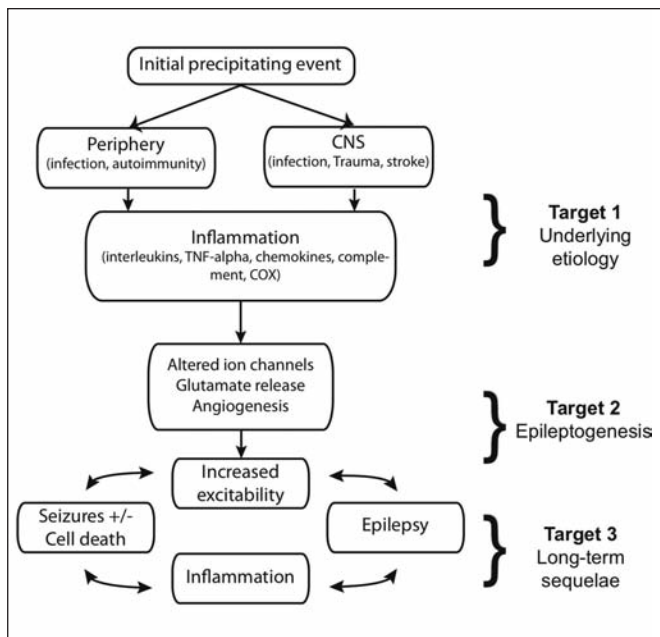
Figure: Possible targets for IVIG in adult epilepsy. Flow chart representing the interactions between the immune system and epilepsy. The steps at which targeting the immune system might be of benefit for treatment of adult epilepsy are highlighted on the right. (Adapted from Vezzani et al 2011[14])

these patients reveals microglial activation and infiltration of leukocytes[34]. Lending further support to a role for inflammation in TLE is a study of 38 patients with adult-onset temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS) which showed that about half of patients had evidence of an underlying autoimmune cause as evidenced either by characteristic magnetic resonance imaging (MRI) findings of limbic encephalitis (progressive hippocampal signal increase and volume change from swelling to atrophy) or by the presence of serum autoantibodies. The remaining cases were found to have an initial precipitating event (e.g. head trauma) or were classified as idiopathic[35]. As well, MTLE-HS can be progressive with increased seizure frequency and worsening neurocognitive deficits over time[36,37], an observation that has led some authors to postulate this might be on the basis of ongoing inflammation[38]. Though kindling might be a driving mechanism in this process, it is also thought that inflammation might contribute to kindling, as will be discussed later[39].

Epilepsy in the presence of autoantibodies

There are also cases of adult epilepsy in which an immune-mediated role in pathogenesis is undeniable. Limbic encephalitis is an autoimmune disorder that can present with temporal lobe seizures, disturbances of behaviour and loss of episodic memory. It can be categorized as paraneoplastic or non-paraneoplastic[40]. In paraneoplastic syndromes, the identified antibodies typically have intracellular targets and are not thought to be pathogenic themselves; instead, T-cell-mediated autoimmunity is thought to

cause the neurologic syndrome[41]. On the other hand, non-paraneoplastic limbic encephalitides are associated with antibodies to neuronal extra-cellular cell membrane components such as voltage-gated potassium channels (VGKC), voltage-gated calcium channels (VGCC) and N-methyl-D-aspartate receptors (NMDAR)[42,43].

These conditions carry a high risk of seizures. Up to 76% of patients with NMDAR encephalitis develop seizures and 6% develop status epilepticus[44] which, rarely, can be refractory to both immunomodulatory and antiepileptic treatments[45]. VGKC-antibody encephalitis has also been associated with the development of the chronic seizures of TLE[46]. In the case of non-paraneoplastic autoimmune encephalitides, the anti-neuronal antibodies are thought to directly cause seizures by inducing changes in neuronal excitability, as evidenced by *in vitro* measurement of hippocampal neuronal firing rate after application of antibodies[47]. These autoimmune encephalitides, given their extracellular targets, also seem to be more responsive to immunotherapy, including steroids, plasmapheresis and IVIG[42]. Use of IVIG in these conditions capitalizes both on its ability to neutralize culprit autoantibodies and its suppression of T-cell-mediated immunity.

Less clear is the link between epilepsy and other autoantibodies. Hashimoto's encephalopathy (also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis) is another autoimmune condition characterized by the presence of autoantibodies directed against thyroid peroxidase or thyroglobulin. It is also associated with a high frequency of seizures, present in 60% of cases as reported in one series[48]. Though the pathogenic role of the thyroid antibodies is less clear, abundant evidence supports the utility of immunosuppression in treating the psychiatric and seizure manifestations. This has been mainly in the form of steroids, but, for refractory cases, IVIG has also been used successfully[49-51].

The role of antibodies has also been investigated in the epileptic population at large. Laboratory studies show higher frequencies of autoantibodies in the serum of epilepsy patients; for instance, in patients with idiopathic epilepsy but no known autoimmune condition, autoantibodies occur more frequently than in controls[52]. In one study of 163 patients with various epilepsy types, anticardiolipin antibodies were present in 19% of epilepsy patients compared to 3% of controls (P= 0.0003)[52,53]. It remains unclear, however, if these antibodies are pathogenic especially given that the effects of anti-epileptic drugs on the immune system could confound these associations.

More relevant to the discussion on treating epilepsy patients with IVIG is the finding that the autoantibodies often considered to be directly pathogenic i.e. those that target extra-cellular neuronal membrane proteins such as VGKC, VGCC and NMDA, are detected more commonly in patients with epilepsy[43,54]. For instance, VGKC, VGCC and glutamic acid decarboxylase (GAD) antibodies have been detected in 6.7% of patients with long-standing epilepsy compared to 0.5% of healthy controls[55] further strengthening previous observations[56]. These recent findings, though not sufficient to support a search for antibodies in all seizure patients, underscore the relevance of the immune system in epilepsy, as incompletely understood as it may be.

THE ROLE OF IVIG IN EPILEPSY: TARGETING A COMMON STEP IN EPILEPTOGENESIS

Evidence of a link between seizures and inflammation

Aside from the etiology-specific potential for IVIG, there may also be a broader role for targeting the immune system in epilepsy, irrespective of the underlying etiology (Figure). Epidemiological evidence for this comes from the observation that fever, the manifestation of a systemic inflammatory state, is the most common cause of seizures in children worldwide. It is thought to lower the seizure threshold by multiple mechanisms: amongst others is the theory that the induction of a pro-inflammatory cascade releases cytokines that may be directly proconvulsant[14,57,58]. Stress and sleep deprivation, other known triggers for seizures, are also associated with the generation of an inflammatory response which may point to one cause underlying their mitigating role in seizure control[59-61].

Elucidating the mechanisms for inflammation-mediated hyperexcitability, a crucial step in seizure generation, has provided proof of concept evidence that there is a link between inflammation and seizures. Experimental research shows that pro-inflammatory cytokines can directly induce neuronal hyperexcitability by altering the function of membrane receptor channels. For instance, tumor necrosis factor (TNF)-α increases expression of the excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptor and promotes endocytosis of gamma-aminobutyric acid (GABA) receptors thereby reducing its inhibitory potential. IL-1β promotes membrane depolarization by enhancing the NMDA receptor mediated inward calcium current. Thus inflammatory cytokines have various proconvulsant effects[39].

A definite association between epilepsy and inflammation has been proven many times over. Experimental evidence, using molecular profiling studies, shows that genes linked to the immune system are up-regulated during epileptogenesis in rodent models[62]. In human epilepsy, evidence of a role for inflammation in epilepsy comes from clinical observations of patients with focal epilepsies related to non-progressive structural lesions not classically thought to be inflammatory[63]. For instance, cortical tubers, the epileptogenic lesions of tuberous sclerosis complex, show prominent inflammatory markers and adjacent alteration of the BBB thus implying activation of proinflammatory pathways[28,64]. Human brain tissue resected from patients with temporal lobe epilepsy and hippocampal sclerosis shows overexpression of various inflammatory cytokines, some of which are thought to have direct proconvulsant effects[39,65]. Positron emission technology, a novel method for demonstrating inflammation, uses tracers for activated microglia and has shown increased uptake in the region of focal cortical dysplasias identified as a seizure focus[29].

What remains less clear is the strength and direction of the relationship between epilepsy and inflammation. Does inflammation promote epileptogenesis? Or do seizures cause secondary inflammation? And if so, does that play a role in kindling and in explaining the long-term sequelae of seizures? (Figure)

Inflammation causes seizures

Whether inflammation causes or predisposes to seizures has been evaluated in rodents by administering proinflammatory molecules, simulating systemic bacterial infections and creating models of chronic inflammation. Although there are some conflicting results attributed to different doses used, overall, the inflammatory state seems to either decrease the threshold for seizures or increase their duration and severity[65]. Perhaps more convincing for a cause and effect association is the evidence drawn from rodent models evaluating seizure propensity following status epilepticus or kindling. In these models, administration of antiinflammatory treatments such as cyclooxygenase inhibitors, anti-cytokines or other immuno-suppressants reduced seizure susceptibility to a proconvulsant. This evidence further supports an important role for inflammation in epileptogenesis[39,66].

Seizures cause inflammation

That seizures cause inflammation is less clear based on clinical observations alone but emerging evidence, both *in vitro* and *in vivo*, shows just that, thus providing another target for immune-modulating therapies such as IVIG. It has been proposed that seizures cause neurons to expose antigens that trigger the immune system; for instance, the emergence of glutamate receptor GluR3 antibodies appears to be secondary to seizure-induced neuronal damage[52]. Studies measuring inflammatory biomarkers in epilepsy patients also confirm that seizures cause activation of the immune system. In refractory epilepsy patients, a time-dependent increase in serum IL-6 occurs following seizures[67] and this increase correlates with the severity of seizures in patients presenting to emergency departments with generalized tonic conic seizures[68]. In addition, the degree of this induced inflammatory response is significant; it has been shown that the effects of activation of the immune system on the brain after a seizure are longer-lasting and more widespread, involving both microglia and neurons, than those of endotoxemia[65]. Thus it seems clear that the causal relationship between seizures and inflammation is bi-directional.

Inflammation as a cause of kindling

The notion that the inflammatory response caused by seizures may play a part in explaining kindling (i.e. that an increasing number of seizures is correlated with an increased risk of recurrent seizures) is supported by experiments in rodent models of kindling in which seizure propensity is reduced by pharmacologically inhibiting the immune response[39]. In fact, immunoglobulin treatment has successfully reduced seizure propensity in cat models of kindled epilepsy,[17] though this effect was subsequently found to be less robust[16].

Inflammation as a cause of seizure sequelae

The secondary inflammatory response caused by seizures could also be invoked to explain the lasting neurologic and cognitive complications of status epilepticus (Figure). Status epilepticus is complicated by chronic encephalopathy and brain atrophy in 6-15% of cases[69]. Interestingly, the most frequent complication of status epilepticus is the development of ongoing seizures, occurring in 20-40% of patients[69]. This is perhaps most

worrisome and frustrating in the case of those patients who present with an otherwise monophasic and treatable auto-immune illness such as Hashimoto's encephalitis[69]. Recent experiments in rodent models have shown that administering cyclooxygenase-2 inhibitors following pilocarpine-induced status epilepticus reduces the burden of hippocampal damage[70], decreases the likelihood of recurrent seizures[71] and also improves learning and memory[72]. Though the link between chronic inflammation and neurodegeneration following status epilepticus is becoming clearer in the literature, the exact therapeutic target is still unknown. Intravenous immuno-globulins again presents an interesting treatment opportunity given its multiple targets in the inflammatory cascade.

Implications for use of IVIG

The above discussion also bears relevance to how IVIG might be used. Should it be offered only in the acute setting to 'break the cycle' of recurrent seizures and refractory status epilepticus? Or should it be used as an ongoing treatment modality to control chronic inflammation, much in the same way it is used in chronic inflammatory demyelinating polyneuropathy or myasthenia gravis? By reserving it as an end of the line treatment, are we missing a critical time window during which it might be most effective? The answers to these questions, again, lie in the exact target of IVIG. Which step(s) of epileptogenesis might be halted by immune modulation?

CLINICAL EVIDENCE FOR IVIG USE IN THE ADULT POPULATION

Most of the literature pertaining to IVIG use in epilepsy is in pediatric populations. The vast majority of patients studied have either West syndrome, Lennox-Gastaut syndrome, Landau-Klefner syndrome, continuous spikes and waves during sleep, Rasmussen syndrome, or, less commonly, focal epilepsy of unknown cause. Though mixed, the findings have been overall promising for the use of IVIG. The Cochrane group recently reviewed this topic[73] and found only one randomized controlled blinded study to include in their systematic review which showed a non-significant positive trend towards reduction of seizure frequency in favour of IVIG treatment ($p= 0.095$)[74].

The remaining studies investigating IVIG use for epilepsy are either prospective self-controlled trials[75-79] or retrospective analyses[80]. They assessed that no reliable conclusion could be reached regarding the efficacy of IVIG for epilepsy and that large-scale randomized controlled trials were still needed. In 1994, a comprehensive review of the evidence looked at 24 open trials, none placebo controlled, involving 368 patients, nearly all children, with intractable epilepsy due to a variety of etiologies[76]. They found that the mean clinical seizure reduction and the mean electroencephalogram improvement were 52% and 45% respectively. Following a review, recent Canadian practice recommendations gave an overall score of C to the evidence for the use of IVIG for intractable epilepsy and emphasized that it should only be used as a last resort[81]. For the most recent full review of the evidence see Mikati et al, 2010[79]. Table 2

Table 2: Summary of studies evaluating IVIG for epilepsy in which adults were included

Study and design	Number of patients (number of adults)	Age range	Epilepsy syndrome	Details of treatment	Outcome and follow up period
Mikati et al. 2010[79] Open label study	37 (not specified)	2-20	West syndrome, Lennox-Gastaut syndrome, and partial localization-related epilepsy*	IVIG 2g/kg divided over 4 days followed by 1g/kg every month for at least 6 months (mean duration of treatment was 15 months). Other antiepileptic medications kept the same.	• 43% had ≥ 50% decrease in seizures ($P= 0.041$) and 15% became seizure-free • The reduction in partial seizures did not achieve statistical significance • Patients not followed beyond treatment discontinuation
Billiau et al. 2007[78] Open label study	13 (1 adult, aged 25)	1-25	Various (focal and generalized epilepsies, including symptomatic and non-symptomatic epilepsies)	IVIG 0.4/kg every 3 weeks for 4 cycles. Other antiepileptic medications kept the same.	• 31% had ≥ 50% reduction in seizure frequency • Follow-up: 6 weeks following last treatment
Vilani et al. 2001[92] Case report	1 (1 adult aged 45)	n/a	Rasmussen's encephalitis	IVIG 2g/kg divided over 5 days monthly for 4 months followed by maintenance with 0.4g/kg monthly	• ≥ 75% reduction in seizures with improved neurological function • Follow-up: 10 months
Hart et al. 1994[93] Open label study	9 (1 adult, aged 40)	3-40	Rasmussen's encephalitis	IVIG 1.2g/kg divided over 3 days monthly for 3 months IVIG treatment either followed or was in conjunction with steroid treatment	• No improvement in the adult patient • Children experienced transitory improvement in seizures
Van Rijckevorsel-Harmant et al. 1994[74] Double-blinded trial	40 (not specified)	2-46	Lennox-Gastaut syndrome, West syndrome, partial epilepsy*	3 groups of patients receiving 100, 250 or 4000mg/kg IVIG per dose for a total of 7 doses given over 6 weeks	• No significant seizure reduction • Sub-group analysis of partial epilepsy group showed seizure reduction ($P= 0.041$) • Follow-up: 6 months
Van Rijckevorsel-Harmant et al. 1986[94] Open label study	7 (not specified)	3-21	Lennox-Gastaut syndrome	3.3g/kg divided over 6 weeks	• 85% of patients experienced a seizure reduction, 1 patient was seizure free

* No further details are provided about the underlying etiology of the seizures.

summarizes the outcomes documented in the studies that included adult patients.

The main limitation in extrapolating from these studies to a more general adult population is that the number of adults enrolled in the studies was small (in some cases unknown) and the few adults included had seizure etiologies more characteristic of a pediatric population than of a typical adult epilepsy population. Another major drawback of the literature on IVIG use for epilepsy is that the details of the regimen (including timing of initiation, dose, frequency and duration) are often unclear and no attempts have been made at standardization. This is important since the etiology of epilepsy in any given patient combined with knowledge of the exact step(s) of epileptogenesis found to be immune-mediated could dictate the optimal timing, frequency and duration of treatment. A last limitation to comparing different studies from the literature lies in the nomenclature used: the definition of refractory epilepsy varies widely from one seizure annually[82] to one seizure weekly[74]. This is a crucial point: the considerable cost and side effect profile of IVIG and the so far weak evidence substantiating its efficacy should limit its use to only the more severe cases, as has been pointed out in recent recommendations[81].

There are numerous reports of IVIG use in patients with limbic encephalitis and seizures where antibodies were detected to VGKC[83-85], NMDAR[44,86], novel cell membrane antigens[87,88], and intracellular antigens[88]. We also found two cases of seronegative limbic encephalitis where IVIG was administered: one had a good response to IVIG[89] but the other remained refractory to all attempted treatments including the five-day course of IVIG[90]. These results are encouraging but responsiveness of seizures to immunosuppression in limbic encephalitis has not yet been studied in a systematic fashion. One limitation of these reports is that IVIG is categorized as one of the immunotherapies thereby grouping it with plasmapheresis and corticosteroids. Another is that seizure outcome is not addressed separately from neuropsychiatric outcome.

We found only one case report of IVIG use for the treatment of refractory epilepsy in an adult patient with structural-metabolic epilepsy[91] but no reports of IVIG use for epilepsies of genetic or unknown causes (excluding pediatric syndromes). Despite this paucity of evidence, IVIG has been proposed as part of a treatment algorithm for refractory status epilepticus of unclear etiology, even in the absence of a documented inflammatory cause[10,11].

Conclusions

Though there is mounting evidence of a role for inflammation in epilepsy, in both the cause and effect of seizures, evidence supporting the use of immunotherapy, and in particular IVIG, to treat seizures is still lacking. It is certain that pharmacologically targeting the culprit step in epileptogenesis would be ideal but this exact step is still unknown. IVIG, when compared to other available immunosuppressants, has a wide reach across the inflammatory cascade, with effects on both the innate and adaptive immune systems, thus making it a potential candidate for treating and preventing not only seizures but also their lasting neurocognitive effects. In addition, it has the practical advantage of being available to most neurologists.

A more satisfactory answer to this conundrum is desperately required so that neurologists can use evidence to guide their decisions. Further research is necessary to better identify which steps in epileptogenesis might be targeted by IVIG and which types of epilepsies might benefit most from immunomodulatory treatment. A better understanding of the mechanisms involved will then allow for more focused controlled clinical trials investigating IVIG use in refractory adult epilepsy.

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