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Immunoglobulin use in childhood epilepsy: Literature review

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***Abstract*---**Background: Epilepsy's aetiology is well-known to include an immune component. Several clinical and laboratory research have discovered abnormalities in epileptic patients' immune system branches when compared to the general population. Such anomalies include immunoglobulin deficiencies (mainly immunoglobulin A and immunoglobulin G2), an increased prevalence of specific human leukocyte antigen types, and alterations in cytokine and interleukin profiles. In people with epilepsy, autoantibodies were discovered against glutamic acid decarboxylase, components of the voltage-gated potassium channel complex, and the N-methyl-D-aspartate, gamma-aminobutyric acid, a-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid, and glutamate receptor three receptors. Immune modulating drugs like corticosteroids and corticotrophin have also been demonstrated to help with seizures. In view of these findings, immunosuppressive medicine has potential as an add-on therapy for refractory epilepsy. Aim: We aimed to evaluate the efficacy of immunoglobulin in childhood epilepsy. Conclusion: Despite the fact that new medications are constantly being developed to treat intractable infantile epilepsy, the refractory rate remains high. Despite several investigations on the subject, predictive variables for a good intravenous immunoglobulin response have yet to be identified. In some epileptic disorders, such as idiopathic West syndrome and electrical status epilepticus during sleep, intravenous immunoglobulin appears to be beneficial. The favoured candidates for such therapy with electrical status epilepticus in sleep, as well as the underpinning immunologic processes that are common to those candidates and affected by this agent, are still being investigated.

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Introduction

Epilepsy has a well-known immunologic aspect in its pathogenesis [1]. Several clinical and laboratory studies found differences in numerous immune system branches in epileptic patients compared to the normal population. Humoral deficits (mostly immunoglobulin A and immunoglobulin G2), an increased incidence of certain human leukocyte antigen types [2], and changes in cytokine and interleukin profiles are examples of such abnormalities [3-5]. Autoantibodies against glutamic acid decarboxylase, components of the voltage-gated potassium channel complex, and the N-methyl-D-aspartate, gamma-aminobutyric acid, a-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid, and glutamate receptor three receptors were found in individuals with epilepsy [6,7]. Seizures have also been shown to respond to immune modifying medications such corticosteroids and corticotrophin. Immunosuppressive medication shows prospective as an add-on therapy in cases of refractory epilepsy in light of these findings. [8]

The therapeutic mechanism of intravenous immunoglobulin:

In a growing variety of autoimmune and inflammatory illnesses of the central nervous system, intravenous immunoglobulins are used. Intravenous immunoglobulin's therapeutic mechanism in the central nervous system is unknown. Immunoglobulins cross the blood-brain barrier and inhibit pathogens, host lymphocytes, autoantibodies, complement pathway chemicals, and proinflammatory cytokines, as well as enhancing the activity of natural killer cells in the CSF fluid [9,10]. The overall consequence is a downregulation of the immune system, which disrupts brain structures.

The role of intravenous immunoglobulin in epilepsy:

Péchadre et al. [11,12] were the first to discover the use of intravenous immunoglobulin in epilepsy by chance in 1977. Since then, a number of modest studies have looked into the use of intravenous immunoglobulin in the treatment of epilepsy, mainly in the context of mixed seizure subtypes and epileptic syndromes. There are no solid data on the therapeutic efficacy of intravenous immunoglobulin in the treatment of epilepsy, and there are no clear indicators as to which cases might benefit. Although the specific mechanism of intravenous immunoglobulin activity is unknown, given the immunologic basis of their action, it is fair to believe that intravenous immunoglobulins can help control seizures in those subtypes of syndromes where immunologic dysfunction is present.

The efficacy immunoglobulin in epilepsy: an issue of growing interest

Most studies that investigated the efficacy of intravenous immunoglobulin treatment for childhood epilepsy were performed in small series of patients. In a review by Billiau et al., the overall success rates emerging from different studies were extremely variable, ranging from none to 64% for the full resolution of seizures, and from none to 100% for partial response (which they defined as a

50% improvement) [13]. In an open-label prospective study of 37 children with refractory epilepsy by Mikati et al. [14], >50% improvement was achieved in 43% of the children, including 15% who became seizure-free.

A recent Cochrane database review [15] described only one study fitting the authors' inclusion criteria. It was a randomized, add-on, double-blind, placebo-controlled multicenter study by Van Rijckevorsel-Harmant et al. [16]. It included patients with all seizure types and failed to indicate any benefit of intravenous immunoglobulin compared with the placebo-treated group for any seizure type. Rasmussen encephalitis is the prototype of epilepsies, with an immunopathogenetic mechanism that exhibits evidence of chronic inflammation processes. New treatments, especially with immunomodulatory drugs, are being investigated in an attempt to decelerate the neurologic deterioration and postpone the need for hemispherectomy. Several authors reported that intravenous immunoglobulin treatment exerts a sustained effect in controlling seizures and in improving neurologic and cognitive function in affected adult patients [17,18]. Hart el al. [19] performed a study on nineteen patients with Rasmussen encephalitis. Seven of nine patients who received intravenous immunoglobulin (including two who concomitantly received steroids) demonstrated substantial improvement in seizures, whereas the effect was temporary in three others. Some reports support the idea that intravenous immunoglobulin may be of some benefit in children, but less prominently than in adults. Granata et al. [20] administered intravenous immunoglobulin to ten children and to one case of adult-onset Rasmussen encephalitis. A dramatic effect was observed in the adult. His seizure frequency declined by 75%, his epilepsia partialis continua ceased, and the neurologic deficits improved. However, seizures decreased by 50% and the neurologic deficits mildly improved in only two of the children. The authors recommended the administration of intravenous immunoglobulin as a first-line therapy in the acute and long-term management of adult-onset disease, but as a third-line treatment in childhood- onset disease. Fayad et al. [21] and Lagae et al. [22] described the first two cases of Landau-Kleffner syndrome that responded to intravenous immunoglobulin. Those authors administered intravenous immunoglobulin to two children who had not responded to conventional antiepileptic drugs and corticosteroids, and the results demonstrated an arrest in language deterioration, coinciding with the control of electroencephalogram discharges. This dramatic effect lasted for months and was replicable when relapses occurred. Intravenous immunoglobulin for this indication was also reported by Mikati and Saab to be remarkably effective when administered as first-line therapy in a toddler [23]. Not all reports have described promising results. Intravenous immunoglobulin exerted no impact in a prospective study on three children with Landau-Kleffner syndrome [24]. Landau-Kleffner syndrome is partly explained by an immunologic mechanism, based on the presence of autoantibodies to myelin and serum immunoglobulin G antibodies to brain endothelial cells in some cases [25,26]. Another patient, like the two previously mentioned patients [21,23,27], exhibited no structural central nervous system abnormalities, and an immunologic basis for his epilepsy had also been suggested.

Febrile infection-related epilepsy syndrome is a clinical condition characterized by refractory status epilepticus with multifocal seizures that suddenly occur in

otherwise healthy children. Patients deteriorate quickly into severe neurologic disability or death [28]. The trigger leading to the catastrophic cascade remains an enigma. A preceding history of febrile illness is usually recalled, but no pathogens are identified. The discovery of several autoantibodies in these patients implies an inflammatory/immunologic mechanism [29]. In a recent multicenter study by Kramer et al. [28] on a cohort of seventy-seven patients diagnosed with febrile infection-related epilepsy syndrome, only two of twenty-nine patients who received intravenous immunoglobulin demonstrated a positive response. Based on those findings, we conclude that intravenous immunoglobulin fails to influence the natural history of this condition.

Several authors observed that intravenous immunoglobulin was very useful in the subgroup of children with idiopathic West syndrome, but not in symptomatic cases. Ariizumi et al. [30] reached a conclusion similar to that. In their study, all six patients with cryptogenic West syndrome demonstrated complete remission, whereas only one of five patients with symptomatic West syndrome achieved partial improvement, and two others achieved a transitory effect with recurrence. In other studies, the difference between the symptomatic compared with cryptogenic cases in response to intravenous immunoglobulin was less clear and even contradictory. Mikati et al. [14] observed no statistically significant difference in the rate of response to treatment between symptomatic and cryptogenic epilepsy, although they combined West syndrome with Lennox- Gastaut syndrome and partial epilepsy in their study population. Intravenous immunoglobulin resulted in a response of only 22% in their group with West syndrome. Espinosa Zacarías et al. [31] reported what they termed satisfactory results with intravenous immunoglobulin as add-on therapy in four girls with symptomatic West syndrome and one boy with Lennox-Gastaut syndrome. A study of 23 patients by Echenne et al. [32] included nineteen with West syndrome and four with Lennox-Gastaut syndrome. Only five patients achieved complete remission, and four of them manifested severe brain lesions. The positive results of intravenous immunoglobulin in West syndrome and the tolerable side effects of this therapy may enable intravenous immunoglobulin to replace adrenocorticotropic hormone therapy. Immunologic involvement was hypothesized to play a role in West syndrome. Montelli et al. performed several studies that demonstrated cell- mediated and humoral deficiencies in West syndrome and Lennox-Gastaut syndrome [33,34]. The mechanisms by which intravenous immunoglobulin modifies immune dysfunction remain to be elucidated.

A favorable response was elicited with improvement rates ranging from 20-85% in the few investigations performed in patients with Lennox-Gastaut syndrome (those patients were combined with patients manifesting West Syndrome in most of the studies) [35-38]. Gross-Tsur et al. [37] treated nine children, eight of whom manifested Lennox Gastaut syndrome. Four children achieved complete remission, and another three achieved a partial response. Van Engelen et al. [39] performed an add-on uncontrolled pilot study in a group of fifteen children. Those authors demonstrated that immunoglobulins penetrated into the cerebrospinal fluid and exerted the remarkable effect of reducing clinical seizures in 11 of 12 children. Epileptic discharges in electroencephalogram tracings and psychomotor development improved in all twelve patients. These results suggest that

intravenous immunoglobulin in Lennox-Gastaut syndrome may demonstrate a valuable effect.

The application of intravenous immunoglobulin in patients with electrical status epilepticus during sleep had not been previously recognized. However, a 33% success rate was previously reported in a multicenter study of Kramer et al. [40] (seven patients were included both in that study). In a prospective study by Arts et al. [24], one of three children demonstrated neuropsychologic improvement, although the electroencephalogram findings remained severely abnormal. Although immunologic processes are not known to contribute to the evolution of electrical status epilepticus during sleep, corticosteroids were observed to be useful in its treatment [40].

Conclusion and Recommendations

Although novel drugs are continually emerging to treat intractable childhood epilepsy, the refractory rate is still considerably high. Despite the many studies on these issues, predictive factors for a successful response to intravenous immunoglobulin remain to be determined. Our study supports the use of intravenous immunoglobulin in selected epileptic syndromes, and especially idiopathic West syndrome and electrical status epilepticus during sleep. Answers regarding the preferred candidates with electrical status epilepticus in sleep for such treatment, and the underlining immunologic processes that are common to those candidates and that are disrupted by this agent, await further investigation.

Contribution of authors
All authors shared in designing the study, collecting, analyzing, and interpreting the data then read and approved the final manuscript.

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