Evidence of Immune changes in the brain in some patients with epilepsy

- Humoral deficiencies (mainly immunoglobulin A and immunoglobulin G2)
- Increased prevalence of certain human leukocyte antigen typing [2]
- Alterations in cytokine and interleukin profiles
- Specific autoantibodies in patients with epilepsy targeted to:
  - Glutamic acid decarboxylase
  - Components of the voltage-gated potassium channel complex
  - N-Methyl-D-Aspartate
  - Gamma-aminobutyric acid
  - a-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid
  - Glutamate receptor 3 receptors

Mechanism’s of action

- The therapeutic mechanism of intravenous immunoglobulin in the central nervous system remains unclear.
- Immunoglobulins reach the cerebrospinal fluid by crossing the blood-brain barrier, where they exert their action by suppressing:
  - Pathogens
  - Host lymphocytes
  - Autoantibodies
  - Complement pathway substances
  - Proinflammatory cytokines
- Increasing:
  - Activity of natural killer cells.
- The net effect involves a downregulation of the immune cascade that causes disruption to brain structures/seizures.

Why think about immunoglobulin therapy?

- Epilepsy as a cause of brain inflammation or response to inflammation
- Infectious or post-infectious cause of epilepsy...Rasmussen’s encephalitis
- Paraneoplastic syndromes

Where has IVIG been used?

- West Syndrome
- Electrical Status Epilepticus of Slow Wave Sleep
- Rasmussen’s Encephalitis
- Lennox-Gastaut Syndrome
- Febrile Infection Related epilepsy syndrome
- Landau-Kleffner syndrome
- Myoclonic-Astatic Epilepsy (Doose syndrome)
- Other undefined epileptic syndromes

Cochrane Database Literature Review

- No randomized controlled trials that investigated the effects of IVIg monotherapy for epilepsy.
- One study (61 patients) was a randomized, double-blind, placebo-controlled, multi-center trial which compared the treatment efficacy of IVIg as an add-on with a placebo add-on in patients with refractory epilepsy.
- There was no significant difference between IVIg and placebo in 50% or greater reduction in seizure frequency.
- The study reported a statistically significant effect for global assessment in favor of IVIg.
- No adverse effects were demonstrated.
Double Blind Study

- 61 pts
- 46 partial refractory epilepsy
- Statistical difference
- No dose effect

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responders</th>
<th>Non Responders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>IVIG</td>
<td>21</td>
<td>19</td>
<td>40</td>
</tr>
</tbody>
</table>


Mikati Open label trial

Forty-three percent had a >50% decrease in seizure frequency
15% became seizure free

<table>
<thead>
<tr>
<th>Seizure Frequency</th>
<th>P value</th>
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<tbody>
<tr>
<td>Before IVIG</td>
<td>On IVIG</td>
</tr>
<tr>
<td>West Syndrome</td>
<td></td>
</tr>
<tr>
<td>211 ± 237</td>
<td>169 ± 249</td>
</tr>
<tr>
<td>Lennox Gastaut Syndrome</td>
<td>271 ± 355</td>
</tr>
<tr>
<td>Generalized Epilepsy</td>
<td>246 ± 317</td>
</tr>
<tr>
<td>Partial Epilepsy</td>
<td>191 ± 437</td>
</tr>
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</table>

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West Syndrome

- ¾ idiopathic responded
- None of 10 symptomatic cases responded

Lennox Gastaut Syndrome

- Add on placebo-controlled, single-blind trial.
- Ten patients, aged to 14 years, with insufficient response to conventional anticonvulsive therapy received placebo and Sandoglobulin 400 mg/kg two times each with an interval of two weeks.
- The washout period was four weeks and the total observation period 16 weeks, during which patients trial epilepsy frequency and type of seizures EEG, in vitro lymphocyte transformation test and IgG subclasses were evaluated before and after active treatment.
- The remaining 8 children, who had either a high or a low but variable seizure frequency showed no change as EEG and their general condition was unaffected.
- Intravenous immunoglobulin had an immediate and pronounced effect on breakthrough seizure activity and a simultaneous neurophysiologic effect in 3 of our patients with Lennox-Gastaut syndrome.

Electrical Status Epilepticus of Slow wave Sleep

- 1/6 complete resolution
- 5/6 partial resolution

Landau-Kleffner Syndrome

- Six children
- Three had LKS, and three had CSWS syndrome.
- No patient had seizures during IVIg treatment and follow-up.
- Their electroencephalography (EEG) findings did not improve.
- Neuropsychological improvement occurred in one child with CSWS syndrome.
- Three children did not show any beneficial effect; they were subsequently treated with steroids, one with a clearly positive result.
- We conclude that successful treatment of LKS and CSWS syndrome with IVIg occurs occasionally.
- IVIg treatment and clinical improvement cannot be denied in individual patients, its real value remains to be determined.
FIRES

- The 77 patients presented with prolonged refractory status epilepticus.
- A preceding febrile infection had been reported in 96% of them. Treatment modalities included antiepileptic drugs (a median of 6x), intravenous immunoglobulin (IVIG, 30 patients), burst-suppression coma (BSC, 46 patients), and other less conventional agents.
- There was no evidence of efficacy for those treatment modalities except for IVIG (two patients), a ketogenic diet (one patient), and a prolonged cycle of barbiturate coma (one patient).
- Nine patients (11.7%) died during the acute phase of FIRES.
- Only 12 of the 68 surviving patients (18%) retained normal cognitive level, but most of them had learning disabilities.
- Sixty-three patients (93%) had refractory epilepsy at follow-up. Cognitive levels at follow-up were significantly associated with duration of BSC (p = 0.005) and younger age at FIRES onset (p = 0.02).


Rasmussen Encephalitis

- Autoimmune response to Anti Glu R3 antibodies
- 19 patients with Rasmussen’s syndrome (chronic encephalitis and epilepsy)—a rare progressive disorder of unknown etiology causing focal epilepsy, hemiparesis, and intellectual deterioration
- With intravenous immunoglobulins, high-dose steroids, or both, to control seizures and improve the end point of the disease.
- Ten of 17 patients receiving steroids,
- Eight of nine patients receiving immunoglobulins, had some reduction of seizure frequency in the short term.
- Improvement in hemiparesis was slight.


Adult use of IVIG

- Though there is interesting theoretical potential for treatment of refractory epilepsy in adults with IVIG, insufficient evidence exists to support its standard use.

IVIG and Immune therapy

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