CASPR-2 (Contactin Associated Protein-2 antibodies) Related Autoimmune Limbic Encephalitis in an ESRD patient

The Apex Data Base: Apex Kidney Care, Sushrut Hospital and Research Centre.

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Clinical Presentation

- **Co-morbidities**: TYPE II DM/HTN/ESRD (Diabetic Nephropathy)/MHD-2 years

- **Presentation**:
  - 2 months history of:
    1. Weight loss, failure to thrive
    2. Cognitive and speech impairment
    3. Lapses in memory, insomnia

- **H/O CRBSI-Sternotrophomonas Maltophilia**- ceftazidime/levofloxacin was given for 2 weeks.

- **Course**- despite recovery of sepsis, neurologically same

- Additionally-myoclonic jerks, right gaze preference, right eye droop, fasciculations

- Impression-metabolic encephalopathy- Advised daily hemodialysis- However remained neurologically same
CT BRAIN-
Moderate per-
ventricular ischemic changes

PET-CT-within normal limits
EEG-bilateral slowing with no epileptiform activity

CSF STUDIES-R/M-WNL

CSF and serum autoimmune encephalitis workup sent---
Serum Contactin Associated Protein-2 (CASPR) antibodies were positive.
Treatment

• She was initiated on alternate day Intravenous Immunoglobulin (25gm for 5 days) and plasmapheresis.

• In two weeks, she demonstrated a significant improvement with disappearance of most her presenting symptoms.
Discussion
Autoimmune Encephalitis - Overview

- **Autoantibodies**
  - Onconeural (anti-Yo, -Ma2, -CV2)

- **Surface antigen**
  - NMDAR
  - CASPR
  - IGLON5, GluR, LG11, AMPAR*, GABA_A,R*

- **Intracellular antigen**
  - Anti-GAD

**Treatment aims to reduce number of antibodies:**
- Decreased production
- Increased elimination

**First line:** Corticosteroids, IVig, Plex
**Second line (escalation):** Rituximab, CYC
**Tumor control:** Surgery, chemotherapy, radiotherapy

**Pathogenesis:**
- Presumptively due to T cells
- Immunotherapies with limited effectiveness

**Probability of co-existing malignancy:**
- **High**
- **Low**

*High probability of co-existing malignancy reported in literature*
Diagram shows:
CASPR2 localization at the juxta-para-nodal portion in the node of Ranvier, showing its interaction with Contactin-2 forming the voltage gated potassium channel complex (VGKC complex).

Diagram shows: The IgG4 anti-CASPR2 blocking the interaction between CASPR2 and Contactin 2 protein, without activating complement, but disturbing the expression of the voltage gated potassium channel.
### Characteristic Symptoms and Laboratory findings of Limbic Encephalitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Antibodies</th>
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<tbody>
<tr>
<td>Seizure</td>
<td>GABA-BR (~100%), LGI1 (80–100%), GAD (60–100%), CASPR2 (75%), NMDAR* (70%), AMPAR (33%) FBDS in LGI1 (33–67%)</td>
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<tr>
<td>Paroxysmal dizzy spells</td>
<td>LGI1 (14%)</td>
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<tr>
<td>Cramps or neuropathic pain</td>
<td>CASPR2, LGI1</td>
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<tr>
<td>Movement disorders</td>
<td>NMDAR *, CRMP5, Hu, GlyR, GABA-BR, DPPX, CASPR2, Ri</td>
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<tr>
<td>Dysautonomia</td>
<td>NMDAR *, LGI1, CASPR2, GABA-BR, DPPX, GlyR</td>
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<td>GI symptoms (diarrhea)</td>
<td>DPPX</td>
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<th>Laboratory findings</th>
<th>Antibodies</th>
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<tr>
<td>Hyponatremia</td>
<td>GLI1 (~30%), CASPR2 (~25%)</td>
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<tr>
<td>Hyperglycemia</td>
<td>GAD</td>
</tr>
<tr>
<td>CSF pleocytosis + OCB</td>
<td>GABA-BR, GAD, mGluR5</td>
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NMDAR antibody (*), a frequently detected antibody in autoimmune encephalitis, should also be included in antibody survey for limbic encephalitis due to clinical similarity. AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2: contactin-associated protein-like 2; CSF: cerebrospinal fluid; DPPX: dipeptidyl peptidase-like protein 6; FBDS: faciobrachial dystonic seizures; GABA-BR: γ-aminobutyric acid B receptor; GAD: glutamic acid decarboxylase; GI: gastrointestinal; GlyR: glycine receptor; LGI1: leucine-rich, glioma inactivated 1; NMDAR: N-methyl-D-aspartate receptor; OCB: oligoclonal band.
Brain magnetic resonance imaging in autoimmune limbic encephalitis. On coronal fluid-attenuated inversion recovery (FLAIR) image, bilateral $T_2$-hyperintensity of the medial temporal lobes is seen (A, arrows).

(B) Bilateral $T_2$-hyperintensity of the medial temporal lobes is also shown on an axial FLAIR image (arrows). Antibodies targeting contactin-associated protein-like 2 were identified in serum by cell-based assay.
Diagnostic approach to acute or subacute encephalopathy

**Acute or Subacute (<3 months) Cognitive Deficits**
± Seizures ± Psychiatric Symptoms ± Movement Disorders ± Dysautonomia

1. **MRI T2 Mesiotemporal ± T1 BG Hyperintensity**
2. **EEG Temporal Lobe (Slow, Discharges)**
3. **CSF Pleocytosis or OCB**
   - Positive in ≥ 1 of (1)–(3)

**Neuronal Antibodies**
- Cell Surface: LGI1, GABAR, AMPAR, CASPR2, mGlur5, DPPX, GlyR, NMDAR*
- Intracellular: GAD**, Hu, Ma, Ri, CRMP5, SOX1, amphiphysin, AK5

**FDG-PET or Repeat MRI**
- Negative
- Positive

**Differential Diagnosis**
- Infection (HSV, HHV6, VZV, HIV, CJD, syphilis, tuberculosis, borreliosis...)
- Inflammation/Autoimmune (vasculitis/angiitis, Behçet’s disease, sarcoidosis, SLE, Sjögren syndrome)
- Vascular (stroke)
- Seizure or Status Epilepticus
- Metabolic/Endocrine (hepatic, uremic, Hashimoto encephalopathy)
- Nutrition (Wernicke encephalopathy)
- Toxic/Drug (alcohol, lithium...etc.)
- Tumor (glioma, lymphoma)
- Neurodegeneration (Alzheimer disease)

**Tumor Survey**: Tumor Markers, Chest ± Abdominal & Pelvic CT or MRI, Whole-Body PET, Mammography...etc. (According to Tumor Frequency & Association)
# Treatment options for Autoimmune Limbic Encephalitis

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<th>Dose &amp; Duration</th>
<th>Mechanism</th>
<th>Note</th>
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<td><strong>First Line</strong></td>
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| Methylprednisolone | Adult: 1 g daily  
Children: 30 mg/kg/day (max. 1 g) for 3–5 days | Inhibits NF-κB → anti-inflammation | 30 mg/kg/day (max. 1 g) once monthly for 3–6 months |
| IVlg | 2 g/kg in 2 or 5 days | Neutralizes Abs and cytokines, decreases B cells, inhibits complement activation, modulates regulatory T cells | 1 g/kg monthly for 3 months or longer  
Should not be given immediately prior to plasmapheresis |
| Plasmapheresis (PE or IA) | 5–7 exchanges in 10–14 days | Remove Ab |
| **Second Line** | | |
| Rituximab | 375 mg/m² weekly for 4 weeks, or 750 mg/m² (max. 1000 mg/dose) for two doses 2 weeks apart | Anti-CD20 Ab → depletion of B cells and plasmablasts |
| Cyclophosphamide | 750–1000 mg/m² (max. 1000–1500 mg/dose) monthly for 3–6 months | Alkylation agents inhibiting DNA synthesis → suppress B and T cells  
Cause infertility in repeated doses |
| Tocilizumab | 8–12 mg/kg (max. 800 mg) monthly for 6 months | Anti-IL6 receptor Ab → inhibits B and T cells |
| Daratumumab | 16 mg/kg weekly in cycle 1–8, every two weeks in cycle 9–13 | anti-CD38 Ab → depletion of plasma cells  
One case of anti-CASPR2 encephalitis |
| Bortezomib | 1.3 mg/m² on day 1, 4, 8, and 11 of a 21-day cycle, total 3 cycles | Proteasome inhibitor → depletion of plasma cells  
Clinical trial (NCT03993282) |
| **Maintenance therapy** | | |
| Prednisolone | 1–2 g/kg/day once daily or divided for 4 weeks; tapered over several weeks to months | Inhibits NF-κB → anti-inflammation |
| Mycophenolate mofetil (MMF) | Initial 300 mg/m²/day, target 600 mg/m²/day, 1–1.5 g/day, twice daily | Inhibits purine nucleotides → inhibits B and T cells |
Conclusions

• Neurological symptoms in hemodialysis patients are fairly common and generally attributable to infections, vascular disease, metabolic causes, trauma and toxins.

• Auto-immune encephalitis should be considered as a differential diagnosis for subacute to rapidly progressive encephalopathy in a dialysis population especially when accompanied by seizures, involuntary movements, psychiatric features, altered cognition and memory disturbances.
Thank you