AUTOIMMUNE ENCEPHALITIS

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DISCLOSURES

 No financial disclosure

 Evolving evidence

OBJECTIVES

 Review the types of antibodies

 Associate antibodies with clinical syndromes and tumor associations

 Recognize the pitfalls in antibody testing
**ACUTE ENCEPHALITIS**

- Brain inflammation
- < 6 weeks
- Infectious agents most common
- Non infectious – Autoimmune, paraneoplastic

**ANTIBODES**

- Neuronal intracellular antigen
- Cell surface synaptic receptors

**MECHANISMS OF DYSFUNCTION**
CELL SURFACE VS INTRACELLULAR

INTRACELLULAR
- Classic paraneoplastic disorders
- Antibodies not pathogenic, T cell mediated response
- Poor response to immunotherapy
- Association with tumors

CELL SURFACE, SYNAPTIC
- Typical autoimmune disorders
- Antibodies are mostly pathogenic
- Responds to immunotherapy
- Infrequent association with tumors

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CELL SURFACE VS INTRACELLULAR

Cell surface Intracellular

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TUMOR ASSOCIATIONS

- Cell surface or synaptic proteins

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TUMOR SCREENING
Probability depends on various factors
- Antibodies
  - Intracellular like Yo, Hu – about 95%
- Age and gender
  - 12 to 45 yr F NMDA – about 50% Ovarian teratoma
  - >45 M/F NMDA – 25% SCLC, Breast
- Clinical syndrome
  - VGCC LEMS – 50% SCLC
  - VGCC PCD – 95% SCLC

TUMOR SCREENING
- CT chest/abdomen/pelvis
- MRI Breast
- MRI Pelvis
- US testis
- US ovaries
- FDG PET
- Tumor markers like CA 125 not sensitive

ANTIBODY TESTING
- Usually serum testing
- CSF testing can be complementary
- Sometimes Ab may be present only in CSF - NMDAR ab, NMO ab
- False positive

McKeon et al. CSF complement serics for evaluating paraneoplastic antibodies and NMO-IgG. Neurology 2011
ANTIBODY TESTING

- Screening
  - Indirect immunofluorescence testing
- Confirmation
  - Western Blot
  - Cell based assay
  - Immunoprecipitation

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**Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma**

Roberta Violani, MD; Warren Matsu, MD; James Aron, MD, PhD; Donald Zierdtling, MD; Zhong Jiang, MD; and Joey Dafnis, MD, PhD

We report four young women who developed encephalopathic symptoms, seizures, memory deficits, disordered level of consciousness, and central hypoventilation associated with ovarian teratoma. CSF and cerebrospinal fluid (CSF) immunologic abnormalities. These patients received treatment with the tumor or immunomodulators and one died of the disorder. Five other CSF patients with a similar syndrome and response to treatment have been reported. Ten patients in the CSF domain immunoreactivity of reabsorbed were reexposed to the symptom, and atypically, few patients had a similar syndrome and response to treatment. Eleven patients in the symptom, patients usually receive. The treatment and follow-up of the treated subjects suggest that the disorder is directly associated with antibodies.

Ann Neurol 2007/05/394-401

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**Paraneoplastic Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma**

Ann Neurol 2007/06:25-36

- 12 women with ovarian teratomas
- Serum/CSF Ab to cell surface of hippocampal neurons
- GluN1 subunit of NMDAR
NMDAR AB: CASE SERIES OF 577 PATIENTS

- Median age: 21
- Only 6% of males had tumor

NMDAR ANTIBODIES: CLINICAL COURSE

- 30.4% patients
- Associated with prolonged hospitalization

EXTREME DELTA BRUSH
VGKC ANTIBODIES

- Antibodies against voltage gated potassium channel
- VGKCs
  - On membrane of neurons in CNS and PNS
  - Mediate repolarization after an action potential
- First associated with Isaac syndrome, Morvan syndrome

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VGKC ANTIBODIES

- Leucine-rich glioma-inactivated 1 (LGI1)

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VGKC ANTIBODIES

- Contactin associated protein-like 2 (Caspr2)
VGKC ANTIBODIES

- Anti LGI1 antibodies
- Anti Caspr2 antibodies
- VGKC Ab without above 2

ANTI LGI1 ANTIBODIES

- Second most common etiology of autoimmune encephalitis

<table>
<thead>
<tr>
<th>Clinical features of anti-LGI1 encephalitis</th>
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<tbody>
<tr>
<td>Patient demographics</td>
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<tr>
<td>In females (97%)</td>
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<tr>
<td>Age 20–70 years old (94%)</td>
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<tr>
<td>Clinical syndrome: limb encephalitis (99%)</td>
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<tr>
<td>Nystagmus (99%)</td>
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<tr>
<td>Ataxia (99%)</td>
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<tr>
<td>Action tremor (47%)</td>
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<tr>
<td>Cognitive disturbance (99%)</td>
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<tr>
<td>Sleep disturbance (99%)</td>
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<tr>
<td>Antipyretic testing (99%)</td>
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<td>Hyporeflexia (99%)</td>
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<tr>
<td>Brainstem auditory evoked potentials (21%)</td>
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<td>Cardiac rate, blood pressure (42%)</td>
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<td>T-wave inversion (10%)</td>
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<td>CSF IgG increase (63%)</td>
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FACIOBRACHIAL DYSTONIC SEIZURES

- Specific for anti-LGI1 encephalitis
- Present in 50%
- Involuntary contractions of 1–2 seconds, affecting the unilateral arm (or leg) and face
- Occur 40 to 100 times a day
- Often not appreciated by patients and physicians
- Most have no ictal EEG correlates, but long FBDS can be preceded by electrodecremental events, which usually precede the onset of movement by ~500 ms, or a slow frontal wave that is contralateral to the FBDS

ANTI LGI1 ANTIBODIES

- AEDs not effective
- Early immunotherapy in FBDS can prevent progression to LE
- Steroids, IVIG, PE, Rituximab
- ?sustained therapy with Mycophenolate, azathioprine
- 2 yr follow up - 70% favorable outcome
- Case fatality rate - 6-19%
- > 2 yr follow up studies – 27 to 35% relapse rate

ANTI CASPR2 ANTIBODIES

- Rare compared to anti-LGI1 ab, hence limited data
- Myokimia
- Fasciculations
- Muscle cramps
- Hyperhidrosis
- Cognitive decline
**ANTI CASPR2 ANTIBODIES**

- 70 to 90% respond to treatment
- Steroids, IVIG, PE, Rituximab
- Thymoma removal
- Favorable outcome in 73%
- 2 year case fatality rate 10%

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**VGKC ANTIBODIES BUT NEGATIVE LGI1 OR CASPR2 ANTIBODIES**

- Clinical significance of these is unclear
- Few have limbic encephalitis or Morvan's syndrome
- Vast majority have varied clinical manifestations - Creutzfeldt–Jakob disease, psychogenic nonepileptic seizures, REM sleep behavior disorder, MSA, peripheral neuropathy, vasculitis, seizures, mitochondrial disease, periodic paralysis, hepatic encephalopathy, FTD, Lewy body disease, Asperger syndrome and schizophrenia

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**STIFF PERSON SYNDROME**

- Muscle stiffness, rigidity, and painful spasms
- Paraspinal, abdominal, and lower extremity muscles
- Spontaneous or triggered by movement or sensory (tactile, auditory) and emotional stimuli.
- EMG - sustained motor unit activity leading to cocontraction of agonist and antagonist muscles.
- Improvement with sleep, diazepam, Baclofen
ANTIBODIES ASSOCIATED WITH STIFF PERSON SYNDROME

ANTI GAD ANTIBODIES

- Low titres in 1% of healthy people and in 80% of people with type 1 diabetes mellitus
- High titers GAD65 antibodies associated with SPS, Cerebellar ataxia (100 to 1000 times that for type 1 DM)
- Antibodies likely not pathogenic, T-cell mediated
- Evaluate CSF for GAD antibodies

ANTI THYROIDOXIDASE ANTIBODIES

- Hashimoto’s encephalopathy or SREAT
- Unclear pathophysiology
SUMMARY

- Identification of clinical syndrome is very helpful.
- Most antibodies have well defined clinical syndromes associated with them.
- VGKC Ab without LG1 or CASPR2 specificity likely have little value.
- GAD65 Ab in low titers, anti TPO Ab are present in general population.
- Antibodies often persist despite improvement in symptoms with treatment.
- Antibody titers do not correlate with clinical course.

THANK YOU

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