Autoimmune Autonomic Ganglionopathy

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Learning Objectives

- Recognize the characteristic clinical features of autoimmune autonomic ganglionopathy (AAG)

- Understand the pathophysiology of AAG as an antibody-mediated disorder

- Understand the interpretation of ganglionic acetylcholine receptor antibody results
Autonomic failure

Presenting symptom can vary:

- **Syncope & OH** – presents to cardiologist
- **Nausea & constipation** – presents to GI
- **Urinary retention** – urology
- **Dry eyes & mouth** – rheumatology
- **Heat intolerance & fatigue** – endocrinology
- **Blurry vision & pupil abnormality** – ophthalmology
Types of autonomic failure

Multiple system atrophy
Parkinsonism/dysautonomia
Pure autonomic failure
Hypothalamic/brainstem disorders
Inherited dysautonomia
Acute idiopathic autonomic neuropathy
Paraneoplastic autonomic neuropathy
Orthostatic intolerance
Metabolic autonomic neuropathies (diabetes, amyloid)
Subacute autonomic failure

- Previously healthy 50 year old woman
- Had “common cold”
- 4 days later, admitted with nausea, abdominal pain, extremity tingling, lightheadedness and blurred vision
- Xray concerning for small bowel obstruction

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>3 min stand</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>154/84</td>
<td>80/56</td>
</tr>
<tr>
<td>HR</td>
<td>70</td>
<td>69</td>
</tr>
</tbody>
</table>

Exam: Dry mouth, dry skin, dilated/sluggish pupils. Normal strength, reflexes, coordination and sensation
Nerve conduction studies normal
First published cases in 1969 by Young et al.
- Subacute onset of severe autonomic failure, including orthostatic hypotension
- No evidence of peripheral somatic neuropathy
- Preceding “viral” illness in some cases
- Partial spontaneous recovery in many

Initially considered as “pure autonomic” GBS or unidentified autonomic toxin

Young et al. Brain. 1975
Autonomic nervous system

- Preganglionic neurons
- Long parasympathetic preganglionic
- Ganglionic AChR
- Sympathetic (superior cervical ganglia)
Nicotinic acetylcholine receptors (AChR)

- Ligand-gated ion channels

- Muscle AChR (NMJ): $\alpha_1\beta_1\gamma\delta$ (fetal) $\alpha_1\beta_1\epsilon\delta$ (adult)
  Antibody against muscle AChR in myasthenia gravis

- Neuronal heteromeric AChR:
  $\alpha_3\beta_4$ – autonomic ganglia (the ganglionic AChR)
  $\alpha_4\beta_2$ – brain/cortex

- Neuronal homomeric AChR:
  $\alpha_7$ – brain (hippocampus), immune system
  $\alpha_9$ – cochlea
Ganglionic AChR

- Transgenic mice that lack α3 subunit have severe autonomic failure and die prematurely

- Inhibitors of ganglionic AChR (e.g. trimethapham, hexamethonium) cause autonomic failure

- “Hexamethonium man” –
  
  “When he has stood for a long time, he may get pale and faint. His handshake is warm and dry… He is thin because his appetite is modest; his stomach never rumbles… he will suffer from retention of urine and impotence”
Ganglionic AChR antibodies

McKeon et al. Arch Neurol 2009
Li et al. Muscle Nerve 2015

Clinical significance 0.2 nmol/L
Upper limit 0.05 nmol/L

Vernino et al. NEJM 2000
Autoimmune Autonomic Ganglionopathy

- Age ~52 (22-82 years), 65% women
- “Viral” prodrome in about 60% (some EBV)
- Subacute onset (but sometimes more insidious)
- Spontaneous, but incomplete, improvement in 1/3
- **Sympathetic failure**: OH, anhidrosis
- **Parasympathetic failure**: dry eyes/mouth, bladder and sexual dysfunction, fixed HR and fixed pupils
- Prominent GI dysmotility
- Occasional association with MG, thymoma, lymphoma or lung carcinoma (rarely)

*Suarez et al. Neurology, 1994*
*Klein et al. Ann Neurol, 2003*
*Vernino et al. Autonomic Neurosci., 2001*
Autoimmune Autonomic Ganglionopathy

- Neuropathic sx (tingling) in extremities in 25%
- Normal strength, sensation, reflexes and NCS
- CSF protein may be mildly elevated (if checked)
- Marked OH and GI hypomotility (severe constipation) are usual chief complaints (about 70%)
- Urinary retention may occur

- Orthostatic tachycardia without hypotension is NOT AAG
- AAG is rare!

Suarez et al. Neurology, 1994
Vernino et al. Autonomic Neurosci., 2001
# Ganglionic AChR antibodies

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>% positive</th>
<th>Ab levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute AAG</td>
<td>~ 50%</td>
<td>0.5 – 41.0 nM</td>
</tr>
<tr>
<td>Chronic AAG</td>
<td>30 – 40%</td>
<td>0.2 – 5.0</td>
</tr>
<tr>
<td>Paraneoplastic AAG</td>
<td>10 – 20%</td>
<td>0.2 – 20.0</td>
</tr>
<tr>
<td>POTS</td>
<td>&lt; 5%</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Idiopathic GI dysmotility</td>
<td>~ 10%</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>MSA (Shy-Drager)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>5 – 10%</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>MG w/o thymoma</td>
<td>3%</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Neuro disorders w/ thymoma</td>
<td>15 – 20%</td>
<td>&lt; 2.0</td>
</tr>
</tbody>
</table>

*Vernino et al., 2000, 2004, 2008; Klein et al., 2003; Thieben et al., 2007*
Autonomic severity

Ganglionic Receptor Binding Antibody (nmol/L) vs. Composite Autonomic Severity Score

$r=0.59$, $p=0.007$

Vernino et al. NEJM 2000
A more subtle case

- Healthy 39 y/o man took a trip to Phoenix
- On returning home, he noted blurry vision and fatigue
- Over 4 wks, constipation alternating with diarrhea
- Next 3 mos, difficult urination, erectile failure, dry mouth, & excessive sweating in his neck & face
- A few fainting episodes preceded by dizziness
- Because of anisocoria, seen by ophthalmology. CT, MRI and MRA normal
- Neuro exam: normal strength, reflexes, & sensation
- His wife (a nurse) got him some prednisone (60mg)
- Dizziness resolved. Urine & bowel fxn normalized
**Autonomic testing**

- **QSART** - delayed and reduced vol. at all sites
- **Cardiovagal** - Valsalva ratio: 1.5 (nl > 1.5)
  
  DB response: 16 bpm (nl >8)
- **Tilt table test**: Supine 10 min tilt
  
  BP 125/95 99/74
  HR 65 83
  plasma NE 65 pg/ml 114
- Normal nerve conduction studies
- Ganglionic nicotinic AChR antibody:
  
  0.5 nmol/L (nl < 0.05)
### AAG Clinical phenotypes

- **Subacute pandysautonomia (classic)**
  - High ganglionic AChR Ab levels (>1.0 nmol/L)
  - Often monophasic illness with residual impairment

- **Chronic diffuse or limited autonomic failure**
  - Lower Ab levels (0.2 – 1.0)
  - Resembles PAF (but with more GI, bladder and pupil)
  - Cardiac sympathetic innervation intact

- **Lower Ab levels**
  - “neuropathic” POTS (~ 5% seropositive)
  - Idiopathic GI dysmotility (~10%)
  - Ab levels < 0.2 are poorly specific
  - In practice, the majority with low gAChR levels do NOT have autonomic or neurological disorder

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*McKeon et al. Arch Neurol 2009*
*Li et al. Muscle Nerve 2015*
Symptoms suggestive of AAG

- Chronic cases may be difficult to distinguish from degenerative autonomic failure
- No parkinsonism or ataxia (differentiate from MSA)
- Low supine plasma norepinephrine
- GI hypomotility, tonic pupil, bladder dysfunction more common in Ab+ compared to Ab- cases

- Severe OH occurs at Ab level > 1.0 nM
- Tonic pupil prominent in patients with Ab > 2.0 nM

Sandroni et al. Arch Neurol 2004
Gibbons et al. Auto Neurosci 2009
Pupillary fatigue in AAG

Bilateral 2 second stimulus

Pupil diameter (mm)

Patient 1

Patient 2

Patient 3

Patient 4

Redilation of AAG pupil begins BEFORE stimulus ends

Normal redilation begins AFTER stimulus

Criteria to define an autoantibody-mediated disorder

Very few diseases fulfill these criteria*

- Relevant specific autoantibodies
- Replicate disease in animals by active immunization
- Transfer disease to animals by injection of IgG
- Clinical improvement with removal of IgG

* Criteria proposed by Witebsky 1966; Drachman 1990
## Specificity of AChR antibodies

<table>
<thead>
<tr>
<th>Group</th>
<th># pts</th>
<th>Ganglionic AChR</th>
<th>Muscle AChR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAG</td>
<td>32</td>
<td>72%</td>
<td>3%</td>
</tr>
<tr>
<td>MG</td>
<td>74</td>
<td>3%</td>
<td>100%</td>
</tr>
<tr>
<td>Controls</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MG patients rarely have $\alpha_3$ antibodies (2/74)
AAG patients do not have $\alpha_1$ antibodies (1/32)
Thymoma patients may have both

*Vernino et al, J Neuroimm 2008*
*Vernino et al. Clin Cancer Res 2004*
*McKeon et al, Arch Neurol 2009*
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Experimental AAG

- Rabbits immunized against α3 subunit
- Produce high levels of gAChR antibodies
- Seropositive rabbits show autonomic failure
- Weight loss, GI dysmotility
- Reduced HRV
- Urinary retention
- Tonic pupils

*Lennon et al. JCI 2003; Vernino et al. JNP 2003*
EAAG Pupils

Mukherjee et al. Auto Neurosci 2007

UT Southwestern
O’Donnell Brain Institute
**Loss of ganglionic synaptic AChR**

<table>
<thead>
<tr>
<th></th>
<th>MAb4 (AChR)</th>
<th>Synaptophysin</th>
<th>Overlay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td><img src="image1" alt="Control_MAb4" /></td>
<td><img src="image2" alt="Control_Synaptophysin" /></td>
<td><img src="image3" alt="Control_Overlay" /></td>
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<tr>
<td><strong>EAAG</strong></td>
<td><img src="image4" alt="EAAG_MAb4" /></td>
<td><img src="image5" alt="EAAG_Synaptophysin" /></td>
<td><img src="image6" alt="EAAG_Overlay" /></td>
</tr>
</tbody>
</table>

*Vernino et al. JNP 2003*
Ganglionic synapse - SCG

Control rabbit

.... but no structural change in synapse

EAAG

Tajzoy et al. Arch Neurol 2011
Passive transfer of EAAG to mice

- IgG prepared from rabbit serum or human serum
- Mice injected *i.p.* on day 0 with 10-15 mg of IgG
- Mice develop transient dysautonomia
- Peak deficits at day 3-4
- Recovery after day 9; fully recovered by day 21

Control

EAAG

*Vernino et al. J Neurosci 2004*
Direct effect of AAG IgG

Wang et al. Neurology 2007
IgG-mediated active internalization of AChR

Wang et al. Neurology 2007
In vitro exposure to IgG

AAG IgG causes decline in EPSP amplitude

Ganglionic EPSP in mouse SCG

Control human IgG

AAG patient IgG

Avg of 10 cons. EPSP
Post-synaptic deficit - ↓ quantal size

mEPSP control

3 days post injection

Wang et al. Exp Neurol 2010
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Case report

- 43 year old man
- Chronic, progressive autonomic failure (> 10 years)
- Severe OH (syncope in < 30 sec)
- Severe GI symptoms, unreactive pupils, anhidrosis, dry mouth, retrograde ejaculation
- Blood pressure: 137 / 72 mmHg supine
  40 / 20 mmHg after 30 sec standing
- Supine NE low (38.9 pg/ml).
- The baroreflex slope (to PE infusion) was 0 msec/mmHg.

Ganglionic nicotinic AChR antibody: 0.54 nmol/L (nl < 0.05)

Schroeder et al. NEJM 2005
Plasma exchange therapy

Improved:

↑ salivation
↑ bowel function
↑ plasma NE

Able to stand for more than 30 min

Schroeder et al. NEJM 2005
Treatment goals

- Disease modifying therapy.
  – Acute vs chronic treatments
  – gAChR Ab < 1.0 associated with reduced severity
  – Autonomic deficits will persist but aim for symptom improvement – return to work/life
  – Monitor for cancer/lymphoma, especially with lymphopenia

- Symptomatic treatment for OH, bowel, bladder

- Lifestyle modification
  – Diet (small meals), exercise
  – Avoid heat
Autoimmune autonomic ganglionopathy

- An antibody-mediated disorder (in some cases)
- Ganglionic AChR IgG is sufficient to inhibit ganglionic transmission in vitro and in vivo
- Clinical autonomic failure is explained by a (reversible) inhibition of ganglionic synaptic transmission
- Understanding of the pathophysiology can aid in diagnosis and treatment