Botulism and Mimicking Disorders

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Latin botulus, "sausage"

Sausage Poisoning in Württemberg

(1820- clinical Report 155 cases)
J Neurol Neurosurg Psychiatry 2008; 195:559-63

Sausage extracts fed to birds, cats, frogs, etc: created botulism model

"The capacity of nerve conduction is interrupted in the same way as an electrical conductor by rust"

Justus Kerner
Physician and poet
1786-1862

Discovery of Bacillus botulinus in Belgium

Among musicians playing at funeral of 87 y old Antoine Creteur: 1895

34 cases from pickled smoked ham
• Diplopia
• Dysphagia
• Dysphonia
• Dysarthria
• Progressive paralysis

"Highly probable... poison in ham was produced by anaerobic growth of specific microorganisms..."

Emile Pierre van Ermengem
1851-1922
Professor of Microbiology,
University of Ghent

Used with permission from Professor Erbguth of the Nurnberg University
Botulism
Preformed Toxin
Food-borne
Spores germinate => later produce toxin
Infant - 10% honey sold in US contaminated with spores!
Wound - black tar heroin
Hidden - prior GI surgery, Crohn’s, recent antibiotics
Proliferates at pH>5, high water content
low salt, low sugar
Heat 85 °C inactivates toxin; 120 °C to kill spores
Note: boiling renders solutions more anaerobic
Semin neuro 2004; 24:155-63
J Environmen Health 2003; 65:93-2

Botulism Outbreaks in Colorado
Boiling food prior to canning at high altitudes may not provide enough heat to kill all spores.
Water boils at 85 °C at 10,000 feet
Add lemon juice (pH) if canning tomatoes
NEJM 1997; 337:84-90
Baked potatoes wrapped in aluminum foil hazardous: spores not killed by baking in foil wrap. Baking aids spore germination. Foil wrap provides anaerobic environment. Dip not reheated prior to serving after days at room temp. 86% attack rate! - Colorado
JID 1998; 178:1727

Foodborne Botulism 1899-1996 in US
Canada: meat 90,000 cases
USA: 24,000,000 y E mostly
Washington state: 0.43/100,000/y
USA 24 cases/y
0.3 outbreak/y
Food/marin - 20%
A - 38%
B, E - 15% each
B spores more in East;
A spores West and
Two European countries where meat is the most common vehicle.
J Clin Neuromusc Dis 2003; 4:129-49
Substance Abuse and Botulism
3 cases after tea from Peyote previously covered in closed jar 2 months
Ages 40, 42, 72 / Religious ceremony
*NEJM* 1998; 339:203-4
Botulism and *C. botulinum* sinusitis after intranasal cocaine
25 male (2nd use 10 days earlier)
Classic presentation but no GI Sx
Ventilator-dependent 6 mo

Botulism and Bioterror
Toxin: 100,000 more toxic than sarin
1 grm toxin aerosolized: potential to kill 1.5 million
LD 50 0.7-0.9 µg inhaled
Gulf War I
Iraq produced 19,000 liters of concentrated BTX – 3x amount needed to kill entire world's people
*JAMA* 2001; 285:1059-70
*JAMA* 1997; 278:433-5

Action of BoNT: Absorbed in Duodenum, Jejunum
Toxin → Circulating system → Cranial and peripheral nervous system
Bacterial Protease:
-50 kD light chain cholinergic synapses, binding irreversibly to presynaptic receptors
-100 kD heavy chain

- From receptor, toxin transmitted into nerve cell
- LC endoproteases selectively target, cleave 3 components of synaptic fusion complex
- Inactivation of SNARE proteins leads to neurotransmitter blockade

- Soluble -N- ethylnaleimide-sensitive Attachment protein Receptor
**Botulism Toxins – mostly**

**C. botulinum: 150 kDa Polypeptides**

All inhibit Acetylcholine release at neuromuscular junction

- *C. baratii* – only F
- *C. butyricum* – E
- *C. argentinense* – G (associated with sudden death, but not paralysis)

ID 50 estimates:
- Oral - 70 μg
- IV .09-.15 μg


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**Natural History of Botulism**

**Usual Incubation 2-36 hours**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Abdominal cramps</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>Acute</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Descending</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>Flacid muscle</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Paralysis (resp.muscles)</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>Posis</td>
</tr>
<tr>
<td>Posis</td>
<td>Ophthalmoplegia</td>
</tr>
<tr>
<td>Tongue weakness</td>
<td></td>
</tr>
<tr>
<td>Cholinergic Parasympathetic Nerves</td>
<td>inhibited</td>
</tr>
<tr>
<td>Constipation</td>
<td>Pupillary abnormalities</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Alternations in resting heart rate</td>
<td></td>
</tr>
</tbody>
</table>


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**Key Clinical Aspects of Botulism**

- Patients are completely alert
- No (rarely) sensory changes
- Symmetrical C.N./Descending Paralysis
- Preserved Deep tendon reflexes
  - (progressively disappear)
- No fever
- Normal/slow heart rate

Note: the absence of cranial nerve palsies rules out botulism!

Ptosis, facial paralysis, youthful, unlined, inexpressive

[CID 2005; 41:167-73]
**Botulism – 50% Require Respiratory Assistance**

Sudden, unexpected respiratory arrest common
Respiratory failure – almost all early deaths
Median time: symptoms to intubation ~ 1 days
Intubation: 2 to 8 weeks; A>B
Case fatality > 5%; if age >60-90%
1st case of outbreak 25% subsequent cases 4%
Hughes Infectious of CNS 1994
Cost of care $340,000 – 1989

**Severe Botulism with Prolonged Toxemia**

Caused by Commercial Carrot Juice

pH 6.8
Low salt
Low sugar

All 6 – required intubation
5 – Dysphagia
4 – Blurred vision
3 – Dysphonia
3 – Diplopia
5/6 antitoxin within 24 h
5/6 survived
At 1 year: 2 still on vent!

Patient 1 – * 100 mouse intraperitoneal 
LD$_{50}$
Patient 2 – * 100,000 MIPLD$_{50}$ highest ever reported

CID 2008; 47:233-9

**Severe Botulism with Prolonged Toxemia**

Caused by Commercial Carrot Juice

**SERUM SAMPLE**

Botulinum toxin < 18 h
After exposure ~ 160 MIPLD 50/ml
Day 8 ~ 1800 MIPLD 50/ml

Day 12 ~ still > 200 MIPLD 50/ml
Two patients given antitoxin at Day 13, 46 respectively

**CLINICAL LESSONS**

* Collect serum 24 h after antitoxin Rx to determine if toxin still present
* Consider antitoxin Rx even Weeks after exposure if high toxin exposure suspected

CID 2008; 47:249-51
C. Botulinum Type G: Sudden Unexpected Death

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Prodrome</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 M</td>
<td>looked pale 10 pm; 7:30 am found dead</td>
<td>Hemorrhagic edema</td>
</tr>
<tr>
<td>29 M*</td>
<td>nausea midday, dry mouth; found dead in bed</td>
<td>Congested brain</td>
</tr>
<tr>
<td>33 M</td>
<td>3 d. abd pain, i.e. thirsty, dry mouth; found dead 9:30 a.m.</td>
<td></td>
</tr>
<tr>
<td>18 wks M*</td>
<td>SIDS</td>
<td>Interstitial Pneumonia</td>
</tr>
<tr>
<td>45 M*</td>
<td>cough, loss appetite; found dead 3:40 am</td>
<td>bronchopneumonia</td>
</tr>
</tbody>
</table>

* Toxin G found in blood

C. Botulinum toxin in 15% SIDS (n=70)

<table>
<thead>
<tr>
<th>Age(d)</th>
<th>Toxin serum</th>
<th>Sm bowel</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>192</td>
<td>A</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>196</td>
<td>G</td>
<td>G</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td></td>
<td>F/F toxin</td>
<td></td>
</tr>
<tr>
<td>373</td>
<td></td>
<td>C/C toxin</td>
<td></td>
</tr>
<tr>
<td>254</td>
<td>G</td>
<td>G/G tox</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>-</td>
<td>G/G tox</td>
<td></td>
</tr>
<tr>
<td>267</td>
<td></td>
<td>F/F toxin</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>-</td>
<td>B/B tox</td>
<td>B/B tox</td>
</tr>
<tr>
<td>198</td>
<td>F</td>
<td>-</td>
<td>F/F tox</td>
</tr>
</tbody>
</table>

Lancet 1985; (Feb)237-41

Confirming Botulism

Demonstrate toxin: serum (10 ml red top)
Gastric contents, stool (sterile water enema), food
Refrigerate – not freeze
Bioassay in mice – most reliable
Sensitivity: 60% - if within 2 days
44% - if within 3 days
23% - if within 4 days
Some culture/toxin-neg cases may be due to not screening for non-botulinum species

JAMA 2001; 285:2059-70
Antitoxin Therapy

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA approved?</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalent (A/B) equine antitoxin</td>
<td>Yes</td>
<td>CDC</td>
</tr>
<tr>
<td>Monovalent (E) equine antitoxin</td>
<td>No</td>
<td>CDC</td>
</tr>
<tr>
<td>Trivalent A, B, E</td>
<td>Yes</td>
<td>CDC</td>
</tr>
<tr>
<td>Heptavalent (A-G) antitoxin</td>
<td>No</td>
<td>USAMRIID, CDC</td>
</tr>
<tr>
<td>IgG portion cleaved “despeciated”</td>
<td>Yes</td>
<td>CDHS</td>
</tr>
<tr>
<td>Human botulinum immune globulin E</td>
<td>No</td>
<td>CDHS</td>
</tr>
</tbody>
</table>

CDC: 404-319-2888
770-488-7100
USAMRIID, US Army Medical Research Institute of Infectious Diseases
CDHS California Department of Health Services
Disaster Med Pub Hth Preparedness 2007; 1:122-34

Treating Botulism

Early antitoxin therapy essential
T ½ 5-8 days
2% anaphylaxis; 4% serum sickness
If wound associated: Penicillin or Metronidazole
Benefit not proven.
If infant botulism: no antibiotics!
(toxin released after bacterial lysis)
Plasmapheresis – Mixed results
Guanidine, aminopyridine – may improve muscle strength in recovery phase
Meds to avoid: aminoglycoside, clindamycin, Mg-containing meds – aggrivate neuro-muscular disorder.

Intensive Care Med 2002; 28:814
Muscle Nerve 1998; 19:701-10

Electrophysiological Dx Botulism

- Compound muscle action potential (CMAP)
  Low amplitude – 85%
  Mostly proximal muscles
  not predictive
- *Decremental* response on 2-HZ stimulation – defect in N-M transmission, but inconsistent
- *Tetanic* stimulation (20–50 HZ) shows *incremental* response reflecting presynaptic defect. Not reliable
  - CMAP following 10 sec max contraction> 20%
    baseline, lasting minutes. Most consistent

A patient with suspected botulism should be treated ASAP.
Deliver the antitoxin
Call state health department to investigate (CDC has supplies in quarantine stations around the country)
CID 2009; 48:874-5

Differential Diagnosis - Botulism

Guillain Barre Syndrome:
Ascending Paralysis
Sensory Abnormalities/Paresthesias Common
Loss of DTRs; No altered pupillary activity
90% autoantibodies (GQ1b)
Elevated CSF protein
Miller Fisher variant may have ocular, bulbar abnormalities (5%)
but usually prominent ATAXIA!
EP studies – peripheral nerve, not neuromuscular junction
May be history of recent diarrhea (C. jejuni in 25% of GBS)
CID 2009; 44:667-73

Guillian-Barre* variants
- Acute inflammatory demyelinating polyneuropathy - 85-90%
- Miller-Fisher - ophthalmoplegia, ataxia, areflexia 5% U.S./25% Japan
- Acute Motor Axonal neuropathy, Most - prior campylobacter, esp. Japan and China
- Acute sensori motor axonal neuropathy 5-10% U.S. more in China, Japan, Mexico
- Bickerstaff brainstem encephalitis
- Other
- Pharyngeal-cervical brachial: arm weakness, swallowing difficulties
- Paraparesis
- Acute pandysautonomia (responds to IVIG) diarrhea, vomiting, abdominal pain, dizzy, orthostatic, urinary retention, pupils abnormal, decreased sweating, salivation, tearing
- CAN IF CSF cell count ≥ 10 -> screen for HIV!
up-to-date 2010
Bilateral Ocular Paralysis (n=31) – over 13,000 Neuro/Nsgy Cases screened

- Botulism – 1
- Myasthenia – 2
- Other – 3
- Miller Fisher – 13
- GBS – 2
- Midbrain Infarction – 4

- Only 1% with myasthenia and 6% with Botulism had complete ocular paralysis

Arch Neurol 2007; 64:178-80

Myasthenia Gravis/Eton Lambert

- Fluctuating, fatiguable weakness
- MG
- Dramatic (<60 sec) response to Edrophonium Chloride
- Autoantibodies (Acetylcholine receptor AB – 80-90%)
- EMG differentiates
- 5% pernicious anemia, RA, SLE
- 5% thyroid disease
- No myalgia, No autonomic features

EMG does mimic botulism

1 mg test dose
Wait 1 min
2-3 mg bolus
Repeat in min if no response

Fluctuating, fatiguable weakness

EL
- Usually preexisting lung CA
- Improves with repeated/sustained exercise
- Squeeze hand – modest squeeze – > more forceful over next 5 seconds – Lambert’s sign
- No deep tendon reflexes
- Usually No cranial nerves involved

Autoimmune Myasthenia Gravis

Target of attack:
1) skeletal muscle acetylcholine receptor
2) muscle-specific receptor Tyrosine kinase (occasionally)

< age 40: Women:Men 3:1
> age 50: Men >> Women

Diplopia -> High titers anti-AchR antibody
Dysarthria -> 50-75% Thymoma Prosis peak onset age 50
Dysphagia -> of those without anti-AChR antibody 40% have antibodies to MUSK
Dysphonia
The patient has several months of fluctuating diplopia, dysarthria, and dysphagia. The exam shows bilateral ptosis, dysconjugate gaze, and a weak myopathic facies. (B) Thirty seconds after administration of 3 mg of intravenous edrophonium, the patient’s deficits are markedly improved. This response would be considered positive, and supportive of the diagnosis of myasthenia gravis. (C) One minute later, with the patient looking up, the Three minutes later, as medial rectus weakness becomes apparent, (D) Five minutes after infusion, not only has the baseline weakness returned but also the patient now has increased difficulty controlling oral secretions.

Lambert-Eaton Paraneuroplastic Neurological Syndrome

1/10,000 with cancer
1% with small cell CA lung
Must: occur before cancer diagnosis
Onconeuronal antibodies: against tumor and nervous system
Almost all have VGCC-Ab
Mechanism: Reduced ACh release
Lower limb weak 100% weight loss 24%
Upper limb weak 78% Myasthenia Sx
Excessive eyelid elevation after sustained upgaze
VGCC—Voltage Gated Calcium channel

**Tick Paralysis**

Symmetric *ascending* paralysis – over 1-2 days
Tendency to fall
Trunca! Instability
Parathesias common, fatigue, myalgias
Cranial nerves – usually normal
Dilated pupil – U.S. – no; Australia - yes
Find the tick!
No fever
Nystagmus
DTRs – absent, diminished

*Infect Dis Clin N Amer* 2008; 22:397-413

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**Case History: 33 y old male**

2-days: fever, sore throat, ITA
Watery diarrhea, photophobis
39˚, rigid masseters, slowed speech
Difficulty eating, drinking, xs saliva
Brief periods: agitation and lucid calm
WBC 12,000 (85% ♦)
LP: 1120 (85% ♦), P-95; Sug – 70
Day 2: L facial weakness (UMN), bilat ptosis
Incomplete ophthalmoplegia
Normal motor, sensory, DTRs

*CID* 2010; 50:77-9

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**Differential Diagnosis**

1. Tetanus
2. GBS – Miller-Fisher variant
3. Bickerstoff-brainstem encephalitis – GBS variant
4. *Paralytic Rabies*

*CID* 2010; 50:77-9
Flush, heat, and violent pains in the face and head, with a giddiness and increase in weakness, pain extended to the hands and feet.

They imagined their teeth were loose.

Whole limbs became paralytic.

Surgeon Lt. Wm. Anderson - 1774
HMS Resolution under Captain James Cook

Ciguatera Poisoning

Worldwide 50,000 cases annually
90% - acute - within 12 hours of ingesting toxic fish

Practice Neurol 2007; 7:36-22

Herbivorous small fish graze on microalgae and detritus of coral reefs containing dinoflagellates (Gambierdiscus toxicus)

Larger reef fish feed on smaller fish - barracuda, grouper, red snapper, amberjack


Ciguatoxins – Polyether Toxins

Higher Concentrations in viscera, liver, head of fish

No taste or smell

Not deactivated by heat/freezer for 6 mo/cooking/gastric juice

Bind to and modulate voltage -sensitive

Na+ channels

- Membrane depolarization $\rightarrow$ decreasing conduction velocity of sensory and motor nerve fibers

J Pub Health 2006; 28:343-6
Ciguatera Poisoning
Usual Incubation ≤ 12 hours (i-30)

- Acute GI sx
- N, V, D, abd pain
- Cirumoral, limb paresthesias
- Reversal of Thermal sense
- Itching Perception of loose teeth
- Headache
- Myalgia
- Polymyositis
- Arthralgia
- Rash – palms/soles
- Tingles – tongue
- Dysphagia
- Tinnitus
- Osteoporosis
- Analgesia

Treatment of Ciguatera Poisoning
IV 20% mannitol (5-10 ml/Kg) infused slowly over 30-45 minutes
(maybe cause decrease edema in Schwann cells, nodal swelling)

Pract Neurol 2007; 7:316-22
JAMA 1998; 259:740-2
Atropine for Symptomatic Bradycardia
Arch Intern Med 1982; 142:1090-2
Case report: 2 patients responded well to gabapentin
NEJM 2001; 344:692-3

Neurotoxins from Marine Dinoflagellates
Caused by diverse specific interaction with Ion Channels Included with Neurotransmission
- Ciguatera fish Na+ 5
- Paralytic shellfish Na+ 1
- Neurotoxic shellfish Na+5

Marine Drugs 2008; 6:349-71
**Neurotoxic symptoms**

Paralytic SP – Tickling sense of lips, mouth, tongue
numb extremities, GI Sx
Difficulty breathing, sense of dissociation
→ Complete paralysis
→ Respiratory failure And CV shock, death
Neurotoxic SP – Nausea, tingling and numbness of
perioral area
Loss of motor control
Severe muscular pain

**Botulism – Pattern Recognition**

Botulism:
4 Ds
Diplopia
Dysphagia
Dysphonia
Dysarthria
Descending paralysis
Fully alert

Ascending Paralysis:
GBS
Tick paralysis
If weakness/Paralysis + sensory findings:
Ciguatera
Marine toxins
GBS

**Disorders Mimicking Botulism**

Transverse Myelitis
Encephalitis
Polio
Diphtheria
7GBS

GBS
Ciguatera
Marine toxins

Fever

SENSORY FINDINGS

Botulism
Tick paralysis
c
Paralytic/Neurotoxic
d
Shellfish

CSF
Normal
Abnormal

Botulism

Transverse
myelitis
Encephalitis
Summary – Botulism Recognition

Descending Paralysis
Symmetrical Cranial Nerve Defects
Alert and Afebrile
Slow/Normal Heart Rate
Preserved DTRs
No sensory Changes

Approach to Diseases Mimicking Botulism

History: Food, travel, tick bites, fever, rate of progression
Pain, sensory problems

PE: Vital signs, 4Ds, neuro exam – Cranial Nerve disorder?
Look for tick!

LAB: CSF, MRI spine, brain EEG, nerve conduction
Botulism and Mimicking Disorders

<table>
<thead>
<tr>
<th></th>
<th>Botulism GBS</th>
<th>Tick paralysis</th>
<th>Transverse myelitis</th>
<th>Viral Enceph. or polio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>no</td>
<td>rare</td>
<td>no</td>
<td>variable</td>
</tr>
<tr>
<td>Sensory Findings</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Pain</td>
<td>no</td>
<td>rare</td>
<td>yes</td>
<td>variable</td>
</tr>
<tr>
<td>Dilated Pupils</td>
<td>yes</td>
<td>rare</td>
<td>US-rare</td>
<td>no</td>
</tr>
<tr>
<td>CSF Protein</td>
<td>normal</td>
<td>elevated</td>
<td>normal</td>
<td>usually elevated</td>
</tr>
<tr>
<td>MRI</td>
<td>normal</td>
<td>usually normal</td>
<td>normal</td>
<td>abnormal</td>
</tr>
</tbody>
</table>

Infect Dis Clinics N Am 2008; 22:397-403

Diphtheric Toxin
Penetrates into Schwann cells
binding quickly – progressive
deterioration of myelin sheath
Equine antitoxin must be given
on day 1 to have effect
Need to call CDC:
1-404-639-2809
1:100 dilution of scratch test
0.02 ml 1:1000 injection
Then therapeutic dose
If disease <48 h 20,000-40,000 n
nasopharyngeal 40,000-60,000 n
Diphtheric Polyneuropathy

32 Patients with Severe Illness

1990–95 – 125,000 cases (4000 deaths)

Former Soviet Union

Arch Neurol 2000; 57:1438–42
J Neurol Neurosurg Psych 1999; 67:433–8

ONSET

Cervical SC
Fat edema
To clavicle
10/31 – myocarditis

Numbers:

• gingivae, tongue
• Face
• Facial nerve of soft palate
• Paresthesias fingers toes
• Dysthiasis, dysphagia

All CN involved

IX – 100%
X – 88%
XI – 84%
XII – 72%
V – 95%

Prox Quadriparesis
Quadriplegia
Areflexia

Improve?

Vibration↑
CSF Protein
Normal protein
≤ 12 cells

Motor disturbances
peaked – day 5

ONSET

3-5 weeks after onset of diphtheria

Weeks 4-7
sudden decrease in blood pressure

Elevated levels of thallium found

Thallium Poisoning from Eating Contaminated Cake – Iraq, 2008

Thallium: odorless, tasteless heavy metal – rodenticide

10/12 who ate cake were ill (83%)

4/10 died (40%)

• ABD pain
• Vomiting
• Dysphagia
• Within hours

5/10 (50%) neuro Δs
had lower Δs
paresthesias
painful, ascending
limb
neuropathy
spasticity
beginning hair loss

Rx: Prussian blue (ferric hexacyanoferrate)

MMWR 2008; 57:1015–8