Exploring the Relationship between Cyanobacterial Toxins and Human Diseases in Florida

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UF COLLEGES OF MEDICINE, VETERINARY MEDICINE, AND IFAS
UF Emerging Pathogens Institute

- Created in 2006 with $60 million appropriation from Florida state legislature, to conduct basic and applied research on human, animal, and plant pathogens
- Over 200 affiliated faculty members, from 11 UF colleges (including medicine, public health, veterinary medicine, and agriculture)
- Collaborations in over 70 countries, reflecting the global nature of work with pathogenic microorganisms

- Team within EPI, working in collaboration with UF Center for Environmental and Human Toxicology, with substantial expertise with emerging harmful algal species:
  - Studies of ciguatera in Florida and the USVI
  - Studies of Amnesic Shellfish Poisoning/domoic acid in Pacific Northwest
<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CAUSATIVE ORGANISMS</th>
<th>TOXIN PRODUCED</th>
<th>CLINICAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciguatera fish poisoning</td>
<td><em>Gambierdiscus</em> spp. and others</td>
<td>ciguatoxins</td>
<td>Acute gastroenteritis followed by paresthesias and other neurologic symptoms</td>
</tr>
<tr>
<td>Paralytic shellfish poisoning</td>
<td><em>Alexandrium</em> spp. and others</td>
<td>saxitoxins</td>
<td>Acute paresthesias and other neurologic manifestations; may progress rapidly to respiratory paralysis</td>
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<tr>
<td>Neurotoxic shellfish poisoning</td>
<td><em>Karenia brevis</em></td>
<td>brevetoxins</td>
<td>Gastrointestinal and neurologic syndromes; formation of toxic aerosols by wave action can produce respiratory irritation and asthma-like symptoms</td>
</tr>
<tr>
<td>Diarrhetic shellfish poisoning</td>
<td><em>Dinophysis</em> spp.</td>
<td>okadaic acid and others</td>
<td>Acute gastroenteritis, abdominal pain</td>
</tr>
<tr>
<td>Amnesic shellfish poisoning</td>
<td><em>Pseudo-nitzschia</em> spp.</td>
<td>domoic acid</td>
<td>In acute cases, gastroenteritis followed by memory loss, neurologic manifestations; may progress to amnesia, coma, and death; chronic, low-level exposure may result in mild memory loss</td>
</tr>
<tr>
<td>Azaspiracid shellfish poisoning</td>
<td><em>Azadinium</em> spp. and others</td>
<td>azaspiracid</td>
<td>Acute gastroenteritis, abdominal pain</td>
</tr>
<tr>
<td>Cyanobacteria</td>
<td><em>Lyngbya</em> spp.</td>
<td>lyngbyatoxin A, debromaplysistoxin microcystins, BMAA</td>
<td>Swimmers itch, particularly in inguinal area; sore eyes, ears; headache; possibly gastrointestinal symptoms</td>
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<tr>
<td></td>
<td><em>Microcystis</em> spp.</td>
<td></td>
<td>Liver damage; neurodegenerative diseases</td>
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HABS in the United States
(from: National Office for Harmful Algal Blooms, Woods Hole Oceanographic Institute)
HABs of Greatest Concern in Florida

• Ciguatera
  • Illness associated with large, predatory reef fish; most common among fishermen going to Bahamas (34% of cases), Florida Keys (20%)
  • Incidence, 2007-2011:
    • Florida: FDOH confirmed cases 0.2/100K population; with corrections for under-reporting, 5.6 cases/100K population
    • Monroe County: FDOH confirmed cases 3/100K; corrected for under-reporting 84/100K (Radke et al)
  • Diagnosis based on clinical presentation: typical pattern of gastrointestinal and neurologic symptoms

• NSP/Brevetoxin
  • Problems along west and east coast of Florida, with regular environmental monitoring by Florida Fish and Wildlife
  • Low number of reported human cases
  • Clinical symptoms reasonably well described:
    • In association with consumption of shellfish: paresthesias, gastroenteritis
    • Respiratory irritation
      • Exacerbation of asthma in patients with a history of asthma, with drop in FEV₁ (Fleming et al – study of 97 asthma patients on a beach with brevetoxin exposure)
HABS of Greatest Concern in Florida - II

• Cyanobacteria
  • Widespread in U.S./Florida
  • Case reports but no incidence data on linked human illness (not reportable to FDOH)
  • Clinical presentations: diverse and poorly documented
    • Skin irritation
    • Possible liver/renal/gastrointestinal toxins (microcystins)
    • Possible neurotoxins
      • BMAA: neurodegenerative illnesses
      • Saxitoxin: PSP-like syndromes
  • Exposure data extremely difficult to obtain
    • Multiple species/strains, with differing toxin genes and expression patterns
    • Multiple toxins/toxin congeners
UF Center for Environmental and Human Toxicology: Chromatogram showing identification of key toxins by LC MS/MS.
Microcystins

• More than 240 microcystin variants produced by cyanobacteria; MC-LR most common
  • Release occurs predominantly after cell death/lysis

• Primary exposure pathways:
  • Ingestion of contaminated drinking water
    • WHO tolerable daily intake (TDI) of 0.04 ug MC-LR/kg body weight/day
    • Inhalation and dermal contact during recreational activities

• Sublethal doses trigger cell apoptosis through formation of ROS; very high doses cause hepatic necrosis

• Selected outbreak reports:
  • 1878, Australia – lethality in livestock dosed with waterside scum
  • 1981, Australia – link between rise in liver enzymes and use of water from dam during bloom
  • 1980s, China – correlation between liver cancer and microcystin exposure
  • 2002, China – correlation with exposure and colorectal cancer
  • 2016, China – correlation with deterioration in renal function
  • 1996, Brazil – 58% mortality due to liver failure among 131 hemodialysis patients, with microcystins found in water used for dialysis

• Ecologic studies:
  • Zhang et al: significant association between cyanobacteria blooms and non-alcoholic liver disease, at county level in U.S.
  • Labine et al: no association between cyanobacterial blooms and liver cancer in Canada
B-N-methylamino-L-alanine (BMAA) is produced by some cyanobacteria. They are identified in cyanobacterial blooms in Florida (Florida Bay, South Biscayne Bay, Caloosahatchee River), and in fish and shellfish, with concentrations ranging from below assay detection to 7000 ug/g (Brand et al). In studies in non-human primates, caused a “dense” tauopathy, with neurofibrillary tangles, with findings similar to those seen in neurodegenerative diseases, including Alzheimer’s disease, frontotemporal dementia and early stages of ALS.

Selected ecologic studies (all of which have potential problems):
- Association of ALS cluster with New Hampshire lake known to have a history of cyanobacterial blooms, high levels of BMAA in fish
- Association of ALS cluster with coastal lagoon in France that has frequent cyanobacterial blooms
- Possible association between high incidence of ALS among veterans of the 1990-1991 Persian Gulf war and exposure to cyanobacterial toxins in desert dust?
Table 1. Numbers of patients with diagnoses which have been linked with cyanobacteria-related toxins, OneFlorida EHRs 2012-2018.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9-CM</th>
<th>ICD-10-CM</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Non-alcoholic liver diseases</td>
<td>790.4, 570, 571.4</td>
<td>R74.0, K71</td>
<td>525,558</td>
</tr>
<tr>
<td></td>
<td>– 571.9, 572, 573</td>
<td>– K77</td>
<td></td>
</tr>
<tr>
<td>Paralytic shellfish poisoning</td>
<td>988.0</td>
<td>T61.78</td>
<td>305</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>335.20, 335.21</td>
<td>G12.21</td>
<td>3,400</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>331.0</td>
<td>G30.0 – G30.9</td>
<td>98,064</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>332.0</td>
<td>G20</td>
<td>50,902</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease

Age-adjusted incidence rate by zipcode

Hotspots

- Cold Spot - 99% Confidence
- Cold Spot - 95% Confidence
- Cold Spot - 90% Confidence
- Not Significant
- Hot Spot - 90% Confidence
- Hot Spot - 95% Confidence
- Hot Spot - 99% Confidence

Legend:
- 0.0 - 16.2
- 16.3 - 29.8
- 29.9 - 47.6
- 47.7 - 87.3
- 87.4 - 695.6
- Population > 20 and Disease Count < 3
Assessment of Human Health Impact of HABs

• Reasonable understanding of health risk associated with ciguatera, NSP/brevetoxin-producing strains
• Much poorer understanding of human health risks associated with cyanobacteria
  • Paucity of exposure data
    • Not sure which species are causing the bloom
    • Not sure which microcystin is present, at what level, and what its toxicity is
    • Not sure if BMAA is present, and at what level
  • Difficulties inherent in associating exposures with long-term health effects (non-alcoholic liver disease, liver cancer, Alzheimer’s disease, ALS)

We have the tools in Florida to do the necessary research – but research will be expensive, and take time

• Need for careful study of HAB species and toxins present in Florida, and environmental conditions that drive toxin expression
• Need for further pathophysiologic/toxicologic studies to assess potential toxicity of “Florida” strains/toxins
• Need for clinical studies, with carefully matched exposure data
  • Documentation of short-term effects
  • Evaluation of possible long-term effects, making use of state-wide clinical databases linked with exposure data