Cyanobacterial Blooms in New Hampshire: An Environmental Trigger for ALS?

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Cyanotoxins in New Hampshire Lakes - What You Need to Know
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NHDES, Concord NH
Recent media attention spawned after a recent NHDES workshop ...
Amyotrophic Lateral Sclerosis

- ALS affects upper and lower motor neurons.
  - Diagnosis is clinical; there is no test for the disease
- Symptoms: Progressive weakness, “wasting” of muscles, cramps, difficulty speaking/swallowing
- Median age is 55 at diagnosis.
- Average life expectancy 2-5 yrs
- 5-10% of cases are genetically inherited: SOD1 mutation
# How Common is ALS?

To put into perspective: some U.S. statistics

<table>
<thead>
<tr>
<th></th>
<th>INCIDENCE (new)</th>
<th>PREVALENCE (all living)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>5,600 cases/year</td>
<td>30,000</td>
</tr>
<tr>
<td></td>
<td>(~2 per 100,000)</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>similar to ALS</td>
<td>350,000</td>
</tr>
<tr>
<td></td>
<td>(1-2 per 100,000)</td>
<td></td>
</tr>
<tr>
<td>Brain Tumor (all)</td>
<td>41,000 cases/yr</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>(15 per 100,000)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>600,000 new/yr</td>
<td>6,500,000</td>
</tr>
<tr>
<td>Heart attack</td>
<td>610,000 new/yr</td>
<td>7,900,000</td>
</tr>
<tr>
<td>Traumatic brain</td>
<td>1,400,000 new/yr</td>
<td>3,170,000 (disabled)</td>
</tr>
<tr>
<td>injury (all)</td>
<td></td>
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Sources: Up to Date 2009; Courtney et al, Medical Clinics N Am 2009; Central Brain Tumor Registry of the United States (CBTRUS) 2004; AHA Heart Disease & Stroke Statistics 2009; Summers et al, J of Epidemiology 2009.
Clusters of ALS suggest an environmental trigger

- Documented “clusters” of disease
  - Guam, Kii peninsula
  - Veterans from 1st Gulf war

- Other arguments for environmental link:
  - Conjugal couples both developing ALS
  - Higher rates among certain populations (Italian soccer players, smokers)
  - Geographic disparities in disease incidence

- ALS seems to be more prevalent in a few areas within New England ... are there true “clusters?”
Why is it so hard to study environmental causes of ALS?

- **Difficult to obtain patient data:**
  - No national ALS registry! (unlike cancer)
  - No unified medical record system, ALS centers don’t collect the same data & can’t share data!
  - Mortality records may not document ALS
  - Errors in diagnosis

- **Logistics of analysis:**
  - Rare disease
  - Lag time: ALS is chronic and progresses for many years before it is diagnosed
  - Millions of potential environmental exposures; difficult to prove causality
  - Gene-environment interactions, other confounders
  - Disease may occur on a spectrum of other neurological conditions
Mapping ALS in New Hampshire

- Review of DHMC records, family interviews, and community databases
- Dwelling address mapped with ArcGIS Software.
- Adjusted for population density
- What we found:
  - Some areas appear to have higher rate of ALS (Lake Mascoma: estimated 10-25x expected)
  - Rate of ALS appears to double around lakes with past cyanobacteria blooms based on preliminary analysis.

<table>
<thead>
<tr>
<th>State</th>
<th>Total ALS Cases (10 yr)</th>
<th>ALS Rate w/in 1/2 mile buffer*</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT</td>
<td>150</td>
<td>4.0</td>
<td>1.68</td>
<td>0.9 - 3.2</td>
</tr>
<tr>
<td>NH</td>
<td>245</td>
<td>4.4</td>
<td>2.32</td>
<td>1.42 - 3.80</td>
</tr>
<tr>
<td>ME</td>
<td>158</td>
<td>3.1</td>
<td>2.77</td>
<td>1.8 - 4.3</td>
</tr>
</tbody>
</table>

* approximate incidence per year per 100,000 population at risk
ALS in New England

- ALS seems to occur in “clusters”
- Are they true clusters or are they happening randomly?
  - Things in nature cluster by chance
  - Example: throw a handful of coins onto the floor

Did this happen by chance? Did an external force influence where the coins landed?

Unlikely result

More likely

- We are still testing our data to determine if the ALS “clusters” we found are true, statistically significant clusters.
ALS in New England

- One common theme – proximity of ALS cases to certain lakes
  - even after adjusting for population

- Is there a link to lake water or lake “culture”? Or something else common within the community?

- One possible link: neurotoxins made naturally by cyanobacteria.

- We are also investigating other environmental risk factors through a patient risk factor questionnaire.
Linking to the Guam hypothesis

- **ALS-PDC** complex highly prevalent in Guam (100X).
  - ↑↑ prevalence after WWII
  - Natives who leave Guam: risk ↓
  - Immigrants who take up Chamorro lifestyle: risk ↑
- Native Chamorro lifestyle seems to put people at risk.

- Cycad seeds are a staple of the indigenous diet.
  - Cyanobacteria live symbiotically inside Cycads.
  - Seeds are washed to remove toxins, then made into flour.
- **Flying foxes** also eat cycad seeds & are a delicacy.
  - Extinction of native flying foxes correlates with decrease in ALS-PDC.

Source: Cox et al, Proc Natl Acad Sci U S A. 2003
What we know about BMAA (Beta-Methylamino L-Alanine)

- **Non-protein amino acid** made by cyanobacteria; **small** molecule.
  - Stored in free & **protein bound** form.

- **BMAA is neurotoxic**
  - **Mechanism**: binds **glutamate** receptors, generating free radicals and oxidative damage.
  - BMAA targets motor neurons, but also astrocytes (the support cells).
  - Monkey/mouse models show acute neurotoxicity.

- **BMAA has been found in brain tissues** from ALS patients in Guam and Miami.

BMAA hypothesis

In Theory:
Guam: Ingestion of large amounts of BMAA through food chain → high risk of ALS
Elsewhere: chronic exposure to small amounts of BMAA + genetically susceptibility → increased risk of ALS??

Source: Banack et al, J of Ethnopharmacology 2005
Our Research at DHMC/UNH

We know cyanobacteria are prominent in New England so ...

- Can we identify BMAA in our local lakes?
- How might people acquire BMAA?
- Can we detect BMAA in our ALS patients?
- Can we show BMAA actually **causes** ALS?
- Is there something else necessary for ALS to occur (genetic susceptibility, another toxin?)

Our ultimate goal: could we prevent some cases of ALS by determining who is at risk & reducing environmental exposures?
Can we find BMAA in our lakes?

- We collected samples from several regional lakes in 2008, including Lake Mascoma
  - Of note: no fulminate blooms sampled
- We identified cyanobacteria species known to make BMAA.
  - BMAA undetectable in our Mascoma lake samples in 2008
- Low algal yield? (rainy summer & few blooms)
- Fluctuating levels of toxins?
- Sampling methods inadequate?
- Insensitivity of currently available tests for BMAA?
How might people be exposed to BMAA?

- Direct ingestion of water containing a bloom, or use of lake water for drinking.
  - Some residents on lakes DO use lake water for drinking.
- Consumption of fish/shellfish.
  - Data from Miami: BMAA found in high levels in some shellfish, very low levels in fish; but not always present.
- Inhaling aerosols from water-related sports: sailing, boating, jet-skiing.
- Inhaling aerosols from watering lawns, irrigating; household activities (showering, saunas).
- Spirulina or Blue Green algae dietary supplements
  - Other labs have found microcystin, BMAA, and other toxins in these supplements.
  - BMAA found in hair samples of people taking spirulina supplements.

Source: Dr. Paul Cox, personal communication; Dr. Larry Brand, personal communication; CDC: http://www.cdc.gov/hab/cyanobacteria/facts.htm
In Summary: BMAA

1. Cyanobacteria are ubiquitous in New England lakes, rivers, ponds, & oceans
2. Cyanobacteria can make the neurotoxin BMAA.
   - We don’t know what causes the toxin to be produced or what causes the levels to vary in lake water
3. People could be exposed to BMAA multiple ways.
   - How much exposure is needed to cause disease?
4. BMAA is neurotoxic
   ... but we lack a chronic disease animal model
1. BMAA can accumulate in brain tissue....is it a coincidence or it actually causing ALS?
   - Brain tissues from DHMC are being analyzed, hair samples may help ascertain exposure or susceptibility.
2. A susceptibility or synergistic component is likely
   - Genetic vulnerability? Synergistic effect of multiple toxins?
In Summary: ALS in New England

- There appears to be higher rates of ALS near blooms, but spatial association does **NOT** prove causality!
  - Many environmental factors could be associated with ALS but may not cause ALS.
- The BMAA hypothesis is still a hypothesis.
  - **No proven connection** between cyanobacteria and ALS.
- Exposure to BMAA sufficient to cause disease would have to occur over years and genetic susceptibility probably plays a role.
Take-Home Messages

1. **There are no proven** lifestyle modifications that can reduce your risk of developing ALS in the US.

2. **Avoiding blooms** is a good idea because of other health hazards (not because of fear of ALS).
   - No need to move to a new house or otherwise change your lifestyle!
   - State advisories about blooms posted by NH DES have nothing to do with our preliminary research.

3. **Be kind** to your lakes!
   - Don’t dump anything into the lake that you wouldn’t want your family to drink (sewage, garbage, etc.)
   - Don’t drink untreated lake water!

4. **Support** ALS research
   - Help lobby for a national ALS registry
   - Learn more about ALS through [www.als-mda.org](http://www.als-mda.org) and [www.patientslikeme.com](http://www.patientslikeme.com)
Collaborators

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