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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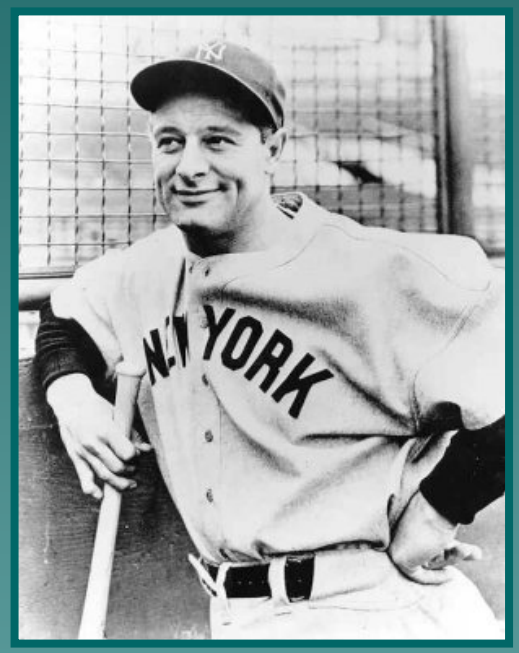
Recent media attention spawned after a recent NHDES workshop …

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

	INCIDENCE (new)	PREVALENCE (all living)
ALS	**5,600 cases/year** ***(~2 per 100,000)***	**30,000**
MS	similar to ALS *(1-2 per 100,000)*	350,000
Brain Tumor (all)	41,000 cases/yr *(15 per 100,000)*	?
Stroke	600,000 new/yr	6,500,000
Heart attack	610,000 new/yr	7,900,000
Traumatic brain injury (all)	1,400,000 new/yr	3,170,000 *(disabled)*

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

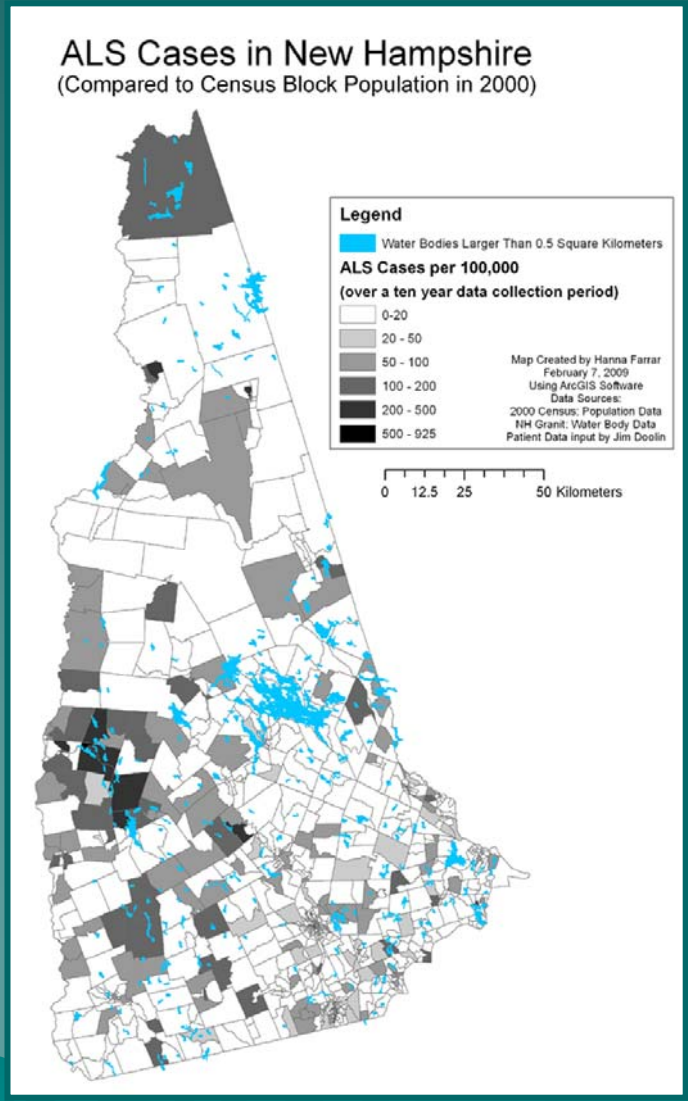
- Documented “clusters” of disease
  - Guam, Kii peninsula
  - Veterans from 1st Gulf war
- Other arguments for environmental link:
  - Conjugal couples both developing ALS
  - Higher rates among certain populations (Italian soccer players, smokers)
  - Geographic disparities in disease incidence
- ALS 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.

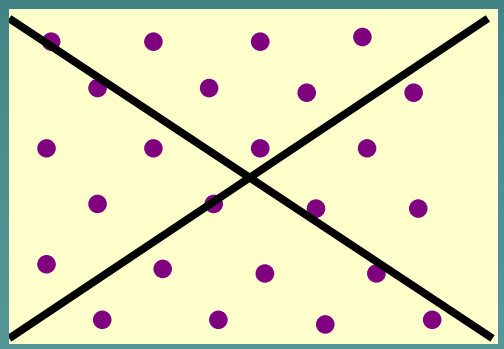


State	Total ALS Cases (10 yr)	ALS Rate w/in 1/2 mile buffer*	RR	95% CI
VT	150	4.0	1.68	0.9 - 3.2
NH	245	4.4	2.32	1.42 - 3.80
ME	158	3.1	2.77	1.8-4.3

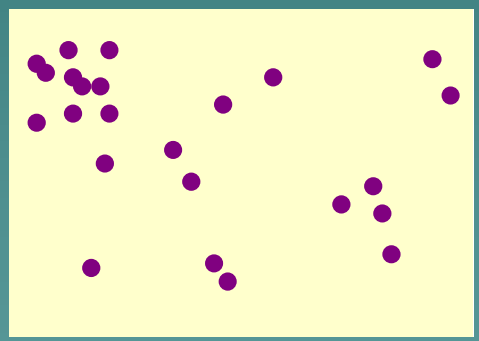
** approximate incidence per year per 100,000 population at risk*

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



Unlikely result



More likely

Did this happen by chance?

Did an external force influence where the coins landed?

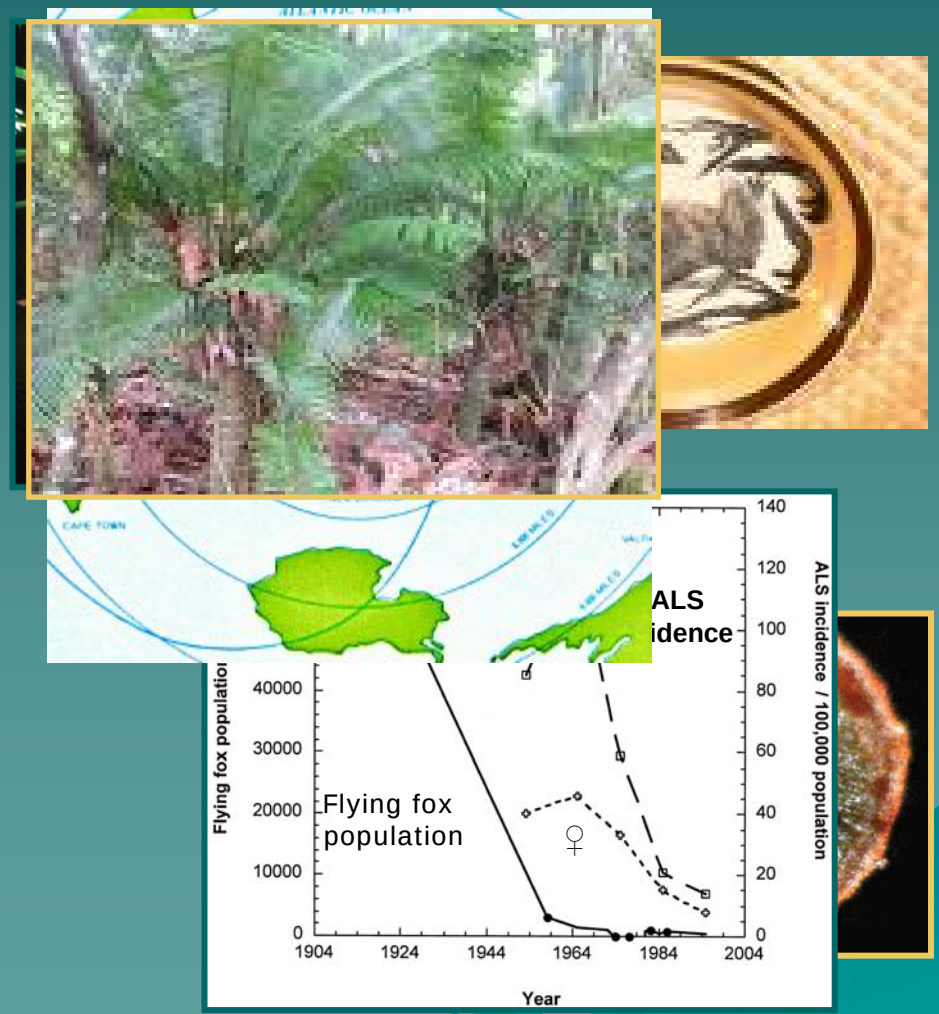
- We are still testing our data to determine if the ALS “clusters” we found are true, statistically significant clusters.

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**.

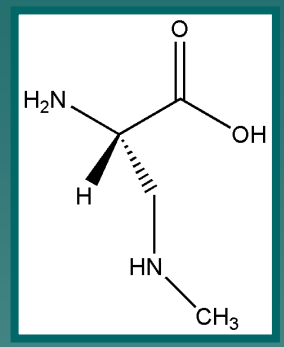
Linking to the Guam hypothesis

- **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)

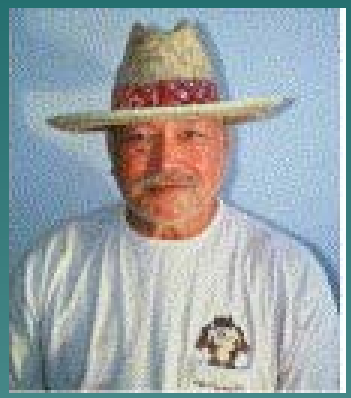


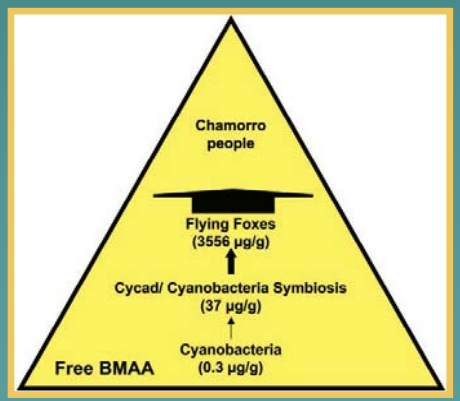
- Non-protein **amino acid** made by cyanobacteria; **small** molecule.
  - Stored in free & **protein bound** form.
- BMAA is **neurotoxic**
  - Mechanism: binds **glutamate** receptors, generating free radicals and oxidative damage.
  - BMAA targets motor neurons, but also astrocytes (the support cells).
  - Monkey/mouse models show acute neurotoxicity.
- BMAA has been found in **brain tissues** from ALS patients in Guam and Miami.

Sources: Loebner D Neurobiol Dis. 2007, Rao SD Exp Neurol. 2006; Murch et al Acta Neurol Scand 2004; Pablo et al Acta Neurol Scand 2009.

BMAA hypothesis

BMAA





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 BMMA 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?



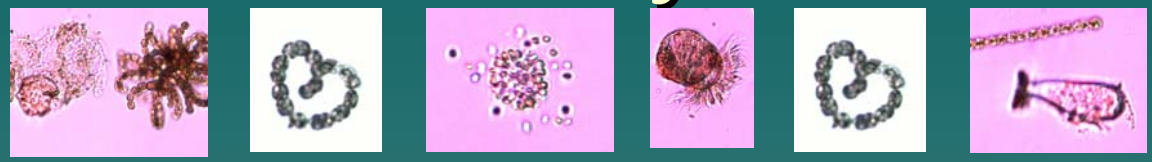



How might people be exposed to BMAA?

- 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 and www.patientslikeme.com

Collaborators

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