ALS and BMAA: Is there a link between epidemiological clusters and cyanobacterial blooms?

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ALS Epidemiology: reported clusters worldwide

Tracie Caller, M.D.
Cyanobacteria and Human Health
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Estimates of ALS incidence

- 1.5-2.5 ALS cases per 100,000 per year in United States and Europe
- Incidence rates appear to be increasing, particularly in industrialized countries
- Risk is slightly higher in men and Caucasians

The mortality rate of ALS in New Hampshire:

- Reported mortality rates for ALS in the United States are lower than incidence rates (approximately 1.5/100,000/year for all ages combined compared to incidence rates of 2/100,000/year), possibly due to underreporting of ALS on death certificates.


<table>
<thead>
<tr>
<th>Year</th>
<th>ALS Counts</th>
<th>Population</th>
<th>Standardized Rate</th>
<th>L 95% CI Standardized Rate</th>
<th>U 95% CI Standardized Rate</th>
<th>Crude Rate</th>
<th>L 95% CI Crude Rate</th>
<th>U 95% CI Crude Rate</th>
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<tbody>
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<td>34</td>
<td>1222017</td>
<td>2.8</td>
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<td>3.4</td>
<td>2.8</td>
<td>1.9</td>
<td>3.8</td>
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</table>
Shellfish/Crab/Shrimp

- Mussels filter 3-8 liters per hour.
- High levels found in mussels in the Baltic and shellfish in Florida
- Bottom dwellers, crabs and shrimp also with high levels in South Florida.
- High levels of BMAA in blue crab in the Chesapeake bay.
Baltic Sea
**Biomagnification**

<table>
<thead>
<tr>
<th>Biomass (C)</th>
<th>Plant</th>
<th>Herbivore</th>
<th>1st Carnivore</th>
<th>2nd Carnivore</th>
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<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
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<td>1000</td>
<td>1000</td>
<td>1000</td>
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<td>(DDT, PCB, Methyl Hg Brevetoxin, Ciguatoxin)</td>
<td></td>
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<td>Protein</td>
<td>1000</td>
<td>100</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Glutamate</td>
<td>1000</td>
<td>100</td>
<td>10</td>
<td>1</td>
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<tr>
<td>BMAA</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
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</table>

**A Cluster of ALS in Guam**

- **Chamorro**: natives of Guam
- **After WWII**, high prevalence of ALS and parkinsonism with dementia (ALS-PDC)
  - Incidence remains 4x expected after moving from Guam
- **Currently**, high incidence of “Guamanian dementia” developing at a late age
- **Why?**
  - Genetics - no clear connection
  - Infectious agent – unlikely
  - Environmental toxin?
  - Cultural? Local cuisine?
Linking to the Guam hypothesis

- Cycad seeds part of the indigenous diet.
- **Bats** also eat cycad seeds & are a delicacy in Guam.
- Bats are consumed whole, have been consumed to extinction.
- Extinction of bats correlates with decrease in ALS-PDC.

*Source: Cox et al, Proc Natl Acad Sci U.S.A. 2003*

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Guam

- evidence of a considerable lag time of many years between exposure to a potential causative agent and development of clinical symptoms
- ALS/PDC developed in 28 Chamorro migrants (24 of whom had onset in the United States, Japan, Germany, or Korea) after periods of absence from Guam of 1-34 years.
- ALS was also documented in nine Filipino migrants to Guam, 29 years after their arrival.

*Garruto Ann Neurol 1980*
Kii peninsula

- Reported prevalence rates have ranged from 100-200 cases per 100,000 persons.
- A large percentage (70%) have a family history of the disease.

Italy

- During the years 1980-2001 death rates and standardized mortality ratios (SMR) for ALS were calculated for all Italian municipalities. 16 clusters with significant high relative risk values (RR) were identified, 12 out of them including only a single municipality.
Conjugal ALS in France

- 9 couples in which both spouses were affected by ALS.
  - Corsica et al; Arch Neur, Vol 60 April 2003
- 8 of the 9 lived in southeastern France.
- The incidence of ALS in France is estimated to be 5 per 100,000; by chance, 0.016 conjugal case may occur each year per 1 million French.

Southern England

- Higher incidence of ALS reported in certain postal codes within Southern England
Finland

• Using a spatial-scan statistic, the researchers examined whether there were significant clusters of the disease at both place of birth and place of death for 1,000 cases of ALS in Finland who died 1985-1995.

• Two significant, neighboring clusters were identified in southeast and south-central Finland at the time of death.

• A single significant cluster was identified in southeast Finland at the time of birth, closely matching one of the clusters identified at the time of death.


Sweden

During the period 1973-1984, 70 males had onset of ALS, corresponding to an average annual incidence of 4 per 100,000 person-years. The number of ALS cases in consecutive 5-year intervals during the study period was significantly elevated for males in the period 1981-1985. This cluster was statistically significant when compared to the rate of ALS in a nearby country.

ALS cluster reported in Skaraborg, Sweden was linked to agricultural work where there is the potential for cyanobacteria blooms in dairy lagoons and dairy product containment facilities


Wisconsin

- Using computer simulation, Taylor showed that cases were not homogeneously distributed throughout the population and that there existed a significant cluster of cases in northeastern Wisconsin. A case-control study by Sienko described a cluster in a small Wisconsin agricultural community bordering Lake Michigan.
  - Taylor J Clin Epidemiol 1989; Sienko Arch Neurol 1990

- The consumption of freshly caught fish at least once per week from Lake Michigan was identified as a statistically significant risk factor \( p < 0.01 \) for ALS
  - Sienko Arch Neurol 1990

Two Rivers, WI: 6 cases
(1975-1983)
1991 Gulf War

- higher incidence of ALS among young servicemen who were deployed to the first Persian Gulf War vs. those not deployed
- Specific geographic locations of troop units were associated with an increased risk for ALS among members of those units.
- Cyanobacteria were discovered in the desert sand.


Interesting, but meaningful?

- Middleborough, MA: 9 confirmed cases of ALS identified in 1969-1985; not statistically significant. (Proctor et al, 1992)
- Boca Raton, Florida Three mail clerks developed and died of ALS over a ten year period in a small town (population: 1200). (Sanders et al, 1980)
- South Dakota: 4 cases of ALS in a sparsely populated county (population 4,000) over a 10-year period in west-central South Dakota, all living within a 15-km radius. (Kilness et al, 1977)
- Reported increase in mortality from ALS among 32,000 civilian employees who had worked at Kelly Air Force Base in San Antonio, Texas 1981-2001; not statistically significant. (Mundt et al. Occup Environ Med 2002)
Environmental influences which have been associated with higher rates of ALS

- pesticides
- heavy metals (lead, mercury)
- selenium
- formaldehyde
- electromagnetic radiation
- head trauma
- Sports such as soccer

**tobacco use**
- Several case control studies reported a 2-3 fold higher risk of ALS with tobacco use
- decreased risk of developing ALS with increasing number of years of smoking cessation

**Mapping ALS in Enfield, NH**
Windsor, VT

Goose Pond
Industry vs. Nature

Algae bloom dispute continues
DEP, mill at odds over phosphorous

Bangor Daily News Bangor, ME - September 1, 2007

Author: Kevin Miller

- Penobscot River: "tensions remain high over the events leading to a massive [blue-green] algae bloom affecting roughly 75 miles of the critically important waterway."
- The Maine Department of Environmental Protection blamed Katahdin Paper Co.’s Millinocket paper mill.
- "Katahdin Paper officials acknowledge that phosphorus discharges from the mill likely contributed to the bloom. But there is some dispute... about what should have happened when phosphorus discharges from the mill increased."
- Phosphorus, more specifically phosphoric acid, is used to whiten the pulp used to make paper.
- "People want brighter paper."
Western Vermont/Eastern New York

Missisquoi Bay, VT
I was stunned with the similarities between your findings on clusters and what happened to my mother and 2 of her friends that lived on the same street here in Annapolis, MD. These 3 individuals all lived within ½ mile of each other on the same street of about 40 middle class homes. They all passed away within 6 years of each other from ALS. My mother was the third to die in 2006. The name of the street is Martins Cove Road, Annapolis, MD, in case you were interested in looking at the street from Google Earth.
“My mother loved to eat, it was one of her favorite things! We’re not sure how she stayed thin. My recollection about blue crabs is that she would occasionally eat steamed blue crabs but more often would eat crab cakes. I think she would eat blue crab about once per month on average. She ate a lot of fish however, especially Flounder, Rockfish (Striped Bass) and Salmon. I would say she ate one of those three maybe once or twice a week. I know that her friend Dave Goldsmith that had ALS first in their neighborhood, loved to eat steamed crabs. He and his wife Fran ate steamed blue crabs all the time and in large quantities.”

Martins Cove Road, Annapolis, MD
GIS using the Census Blockgroup Method

- Recent and previous ArcGIS Mapping: To identify clusters, we have analyzed the spatial distribution of known cases on a census blockgroup level. Within this region, there are at least four spatially distinct clusters of blockgroups with z-scores greater than 2.58 (which is statistically significant) and with six or more excess cases per cluster. For each blockgroup, we calculated an estimate of the normalized excess case count ($c_i$) as follows:

\[ c_i = \frac{o_i - e_i}{e_i} \]

where $o_i$ is the number of observed ALS cases and $e_i$ is the expected number of cases based on the 2007 population and the overall regional rate of 20.7 cases per 100,000 population during the study period (690 cases out of a total population of 3.34 million in our tri-state study area). We then use Anselin’s Local Moran’s I to identify clusters based on their z-scores.

Spatial Clustering in Northern NE

- One cluster is in the Bangor/Orono, ME region. The seven blockgroups in this cluster have ten known ALS cases in a total population of 4770. They are located along the Penobscot River and in close proximity to Chemo Pond and the Graham Lake district. The Penobscot River has a history of serious CB.

- Two clusters are in the Upper Connecticut Valley region of Vermont and New Hampshire. The first of these is an extended cluster of eleven blockgroups around Mascoma Lake and Lake Sunapee, NH, with 18 known cases out of a total population of 13,475. The second cluster consists of three blockgroups in Windsor VT and Plainfield NH, with seven cases out of a population of 379. These cases are located in close proximity to the Connecticut River and to Kennedy Pond, the latter of which has a well-documented history of green scum and pollution, but the biology of the pond is not well known.

- One cluster in northwestern Vermont, near Lake Champlain and two smaller inland water bodies (Shelburne Pond and Lake Iroquois). This cluster consists of six blockgroups with ten known cases out of a population of 9887. Lake Champlain and Shelburne Pond have serious CB and much of the nearby population use the lake for drinking water.
Spatial Associations

- 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

Where to go from here:
- Looking at ALL water bodies – not all blooms are reported.
- What is a meaningful distance to live from a bloom? (0.5 miles was arbitrarily chosen).
- How do we account for mechanism of acquisition?
- Spatial associations do NOT imply causality. \( \rightarrow \text{bench science is still critical} \)
What are Geographic Information Systems (GIS)?

special information systems for handling “geographic information”

http://caligari.dartmouth.edu/~geospace/als/nh_als_test.shtml
Identifying Areas of Elevated Risk for sALS in Northern New England

Nicholas C. Field
Cyanobacteria and Human Health
August 6, 2011

Procedure

- Generate extensive database of sporadic ALS cases in the study region (VT, NH, and ME).

- Integrate the Landscan Global 2008 and 2000 US Census datasets with rate data to generate expected count maps based on age/gender.

- Compare the density of known cases of sALS to the density of the expected cases to identify areas of significant geographic risk.
Expected Rates of ALS

- Case Ascertainment
  - DHMC Records, MDA, Collaborations, Obituaries, Word-of-mouth, Questionnaire

- Nearly 800 patients. 80% coverage?

- Necessary Data
  - Age at Diagnosis
  - Gender
  - Physical Address

Expected Case Mapping - Landscan

- Landscan Global 2008 Dataset
  - High rural resolution.
  - Low urban resolution.
  - Contains population counts.
  - No gender or age information.
Expected Case Mapping - US Census

- 2000 US Census Data
  - Population broken down by age and gender.
  - Areal “census block” units.
  - High urban resolution
  - Low rural resolution

Expected Count Maps - Integration
Expected Count Maps - Integration

- Applying Gender/Age Data from the Census Blocks to the LandScan Grid

- Example: Calculate the number of Males aged 20-29 in a sample LandScan cell.

- Repeated for each age/sex category.

- Makeup of each cell is different.

<table>
<thead>
<tr>
<th>Area in Cell</th>
<th>Total Area of Census Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow</td>
<td>100</td>
</tr>
<tr>
<td>Red</td>
<td>50</td>
</tr>
<tr>
<td>Green</td>
<td>200</td>
</tr>
<tr>
<td>Blue</td>
<td>50</td>
</tr>
</tbody>
</table>
Expected Count Maps - Result

- Higher density of cases in urban areas
  - Burlington, Manchester, Bangor
  - Nashua, Portland, etc.

- Rural areas have very low density.

- Tiny Values (.00001 – 2)

- Separate map for each age/gender demographic (by decade).

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Expected Case Map

- Why all this effort for a “population” map?
  - Important to take into account age and gender.
  - Ex. A small town has 10 nursing homes, thus a population age skewed to the right.
  - ALS is more common in older individuals.

- Sources of Error
  - Incomplete case database.
  - Resolution of LandScan dataset.
  - Missing Census data.
Identification of Areas of Increased Risk

- Calculates density of ALS cases at individual points.

- Monte Carlo Simulation compares the density of a random case distribution to the density of known cases.

- Generates P-values based on the likelihood of the values being found randomly or not.

Areas of Increased ALS Case Density

- Vermont
  - Chittenden, Windsor, and Orange Counties

- New Hampshire
  - Grafton County

- Maine
  - Hancock County
Grafton, Sullivan, and Windsor Counties

- Lake Mascoma and Goose Pond
  - Known algal blooms.
  - Initial site of interest.

- Windsor, VT
  - Two man-made ponds.
  - Pollution from an old Goodyear Rubber plant.

Future Work – Cyanobacteria?

- Some of the regions with a higher incidence are near water bodies with known cyanobacterial blooms.
  - Lake Mascoma
  - Lake Sunapee
  - Lake Champlain
  - Penobscot River

- Further investigation is necessary.
Future Work – Questionnaire

- Address History
  - Proximity to Waterbodies
- Family History
  - ALS and Other Diseases
- Medical History
  - Concussions
  - Medications
  - Smoking
- Social History
  - Military Service
  - Swimming, fishing, sports, etc.

Future Work – Expansion

- Connecticut
  - Yale ALS Center
- Vermont
  - Potentially more complete/accurate dataset due to upcoming UVM collaboration.
- Massachusetts? Rhode Island? Quebec?
- Hepatocellular Carcinoma, Parkinson’s Disease
Collaborators

DHMC
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