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## REVIEW ARTICLE

**Is exposure to cyanobacteria an environmental risk factor for amyotrophic lateral sclerosis and other neurodegenerative diseases?**WALTER G. BRADLEY<sup>1</sup>, AMY R. BORENSTEIN<sup>2</sup>, LORENE M. NELSON<sup>3</sup>, GEOFFREY A. CODD<sup>4</sup>, BARRY H. ROSEN<sup>5</sup>, ELIJAH W. STOMMEL<sup>6</sup> & PAUL ALAN COX<sup>7</sup>

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**Abstract**

There is a broad scientific consensus that amyotrophic lateral sclerosis (ALS) is caused by gene-environment interactions. Mutations in genes underlying familial ALS (fALS) have been discovered in only 5–10% of the total population of ALS patients. Relatively little attention has been paid to environmental and lifestyle factors that may trigger the cascade of motor neuron death leading to the syndrome of ALS, although exposure to chemicals including lead and pesticides, and to agricultural environments, smoking, certain sports, and trauma have all been identified with an increased risk of ALS. There is a need for research to quantify the relative roles of each of the identified risk factors for ALS.

Recent evidence has strengthened the theory that chronic environmental exposure to the neurotoxic amino acid  $\beta$ -N-methylamino-L-alanine (BMAA) produced by cyanobacteria may be an environmental risk factor for ALS. Here we describe methods that may be used to assess exposure to cyanobacteria, and hence potentially to BMAA, namely an epidemiologic questionnaire and direct and indirect methods for estimating the cyanobacterial load in ecosystems. Rigorous epidemiologic studies could determine the risks associated with exposure to cyanobacteria, and if combined with genetic analysis of ALS cases and controls could reveal etiologically important gene-environment interactions in genetically vulnerable individuals.

**Key words:** Amyotrophic lateral sclerosis, BMAA, cyanobacteria, epidemiology, environmental toxicants

**Introduction**

ALS is more common than generally recognized, with an adult lifetime risk of 1 in 400 (1) and annual incidence rate close to that of multiple sclerosis (2). Only about 5–10% of cases of ALS occur in families (fALS), while 90+ % of cases are sporadic (sporadic ALS, sALS) (3). Genetic mutations have been identified in half the families with fALS (4) and 11% of sALS patients (5). Mutations and polymorphisms may increase susceptibility to develop sALS, including SMN1 gene duplication (6), mutations of the angiogenin gene (7), and ataxin-2 intermediate length polyglutamine expansions (8). The paucity of reports of susceptibility genes indicates the importance of environmental factors in sALS, which may act through epigenetic mechanisms (9),

for instance through the C9orf72 hexanucleotide repeat expansion in a non-coding region of chromosome 9 that occurs in one-third of patients with fALS, 7% of patients with sALS, but only 0.2% of controls (4,10).

Exposures to lead, mercury, pesticides and other chemicals have been identified as risk factors for ALS (11–13). Smoking (14,15), sports, particularly professional soccer (16), and head injuries (17,18) have also been implicated as risk factors. The recent negative report concerning American high school football (19) may not apply to professional football. The increased risk of ALS in deployed military might relate to environmental exposures to lead and other toxicants including cyanobacteria (see below) or to head injuries (20–23). ALS risk factors may not

operate independently; the association between ALS and working or living in agricultural areas might relate to exposure to herbicides and pesticides (13,24–27), or to exposure to cyanobacteria in irrigation water (see below). Polymorphisms in critical genes may produce susceptibility to toxins; the association between lead and ALS may be related to certain polymorphisms of the delta-amino laevulinic acid dehydratase gene (12,28), and polymorphisms of the paraoxonase-1 gene are reported increased in ALS patients (29).

### Cycads, cyanobacteria and BMAA

Recently an environmental toxicant,  $\beta$ -N-methylamino-L-alanine (BMAA), has received renewed attention as an environmental risk factor for sALS (30–34). BMAA, a non-protein amino acid (i.e. not one of the 20 amino acids coded in DNA for protein synthesis), was first identified and shown to be neurotoxic over 40 years ago (see below). Most cyanobacterial taxa are able to produce BMAA, though at widely different concentrations throughout their life cycle (35,36). BMAA production by cyanobacteria can be triggered by nitrogen starvation (37,38).

The original clue that BMAA exposure might cause ALS came from the island of Guam; at the end of World War II the frequency of ALS in the indigenous Chamorro people was 100-fold greater than the rest of the world (39). A similar endemic focus was later recognized in the Kii Peninsula, Japan. In both Pacific foci the symptom complex has changed over the last 50 years into a broader spectrum of neurodegenerative diseases, ALS/Parkinsonism-dementia complex (ALS/PDC) (40–46).

Early in the investigation of the Guam focus, flour made from the gametophyte of seeds of *Cycas micronesica* was suspected as the source of the environmental neuro-toxicant. Several toxins were identified in cycad seeds, including BMAA, which proved to be neurotoxic to chicks, rats and monkeys (47). Spencer et al. (48) found that monkeys fed BMAA for 13 weeks developed neurologic signs and neuropathologic changes (49,50). However, Duncan et al. (51) reported that the BMAA doses used by Spencer greatly exceeded the amount of BMAA in cycad flour ingested by Chamorros, leading to abandonment of the BMAA theory for more than a decade.

In the late 1990s, Banack and Cox studying the life-style of Guam Chamorros identified the sources of BMAA, namely consumption of *Pteropus mariannus* (commonly termed flying foxes or fruit bats, which were important in the traditional Chamorro diet) and other animals such as pigs and deer that feed on cycad seeds (52–55). Consumption of *P. mariannus* was significantly correlated with PDC in the Chamorros (55); BMAA was produced by the endosymbiotic cyanobacterium, *Nostoc*, in coralloid roots of Guam *C. micronesica* and bio-accumulated

10,000-fold in *P. mariannus* (54–56); and brains of six Chamorros who had died of ALS/ PDC contained high BMAA concentrations, but not control brains (30,31). They also found BMAA in 8/9 of Alzheimer's disease brain tissues from the Vancouver brain bank of Patrick McGeer (30,31). Borenstein et al. found no association between consumption of fruit bats and increased risk of dementia, but they demonstrated that Chamorros who as young adults collected cycad seeds, prepared and consumed cycad flour, had a significantly increased risk for PDC (33).

Murch et al. (30,31,56) discovered that BMAA was present in 20–50-times higher concentrations in the protein fractions of cycad flour and Chamorro brains than in the soluble fractions. This may explain why Duncan et al. (51) and several later investigators (57–59) rejected the hypothesis that BMAA is a chronic neurotoxin responsible for Guam ALS/PDC, because they did not hydrolyze their samples, measuring only the small amount of BMAA in the soluble fraction and missing the much larger amount in the protein fraction (60).

Murch et al. proposed the hypothesis that chronic dietary intake of BMAA leads to its misincorporation into brain proteins, where it recycles, causing slow neurodegeneration (30,31,56,61). Lee and McGeer (62) criticized the BMAA theory believing that BMAA could not be incorporated into proteins, although nearly half a century earlier Allende and Allende (63) demonstrated that canavanine, another non-protein amino acid, is incorporated into proteins through tRNA<sup>ARG</sup> and arginyl-tRNA synthetase. Support for the Murch et al. hypothesis (30,31) was provided by Mash et al.'s demonstration that <sup>14</sup>C- and <sup>3</sup>H-BMAA are incorporated into rodent brain proteins with a very long half-life (64), and by the Rodgers and Dunlop demonstration that BMAA is misincorporated into proteins in neuronal cell lines via seryl tRNA synthetase, producing protein misfolding, aggregates and cell death (65,66).

Cyanobacteria are ancient and cosmopolitan microorganisms (67), occurring in all environments and often accumulating to harmful densities (45,67–70). Cyanobacterial blooms have increased with eutrophication of water bodies and global warming (71,72), impairing water body and drinking water quality (73). Cyanobacterial blooms are hazardous to health due to their potent cyanotoxins, microcystins, nodularins, saxitoxins, cylindrospermopsins, lyngbyatoxins, anatoxins and lipopolysaccharide endotoxins (74,75). Human and animal illnesses resulting from exposure to cyanotoxins range from mild gastrointestinal illness and skin irritations, to death from acute neuro- and hepato-toxicity (75). Long-term exposure to drinking water contaminated by microcystins has been associated with human primary liver cancer (76–78).

The finding by Murch et al. (30,31) of BMAA in Alzheimer's disease brains was confirmed by Mash et al., who also reported similar BMAA levels in brains of Florida patients with ALS, but not in control brains (79). Brand et al. later found BMAA in the benthic mats of the cyanobacterium *Lyngbya* in the shallow waters around Florida, high BMAA concentrations in bottom-feeding crabs and shrimp, and top-of-the-food-chain sharks and dolphins (80,81). These findings suggest that seafood is a possible source of BMAA in brains of Florida ALS patients.

Studies of areas of high incidence of ALS have supported this conclusion. Investigation of the high incidence of ALS patients in Two Rivers, Wisconsin, found that ALS patients ate fish from nearby Lake Michigan, which is known to have cyanobacterial blooms, more frequently than controls (82). Sabel et al. (83–85) identified regions of increased incidence of ALS in the Finnish Lakeland. The Baltic Sea suffers extensive cyanobacterial blooms, and has BMAA in the blooms and in bottom-dwelling animals that are human food sources (86). Caller et al. identified a 2.3-fold increased incidence of ALS in subjects residing within 0.5 miles of New Hampshire lakes that had current or past cyanobacterial blooms, especially downwind (87,88). Camu et al. identified a significantly increased frequency of ALS in the south of France, particularly in patients who resided near, worked with and ate oysters and mussels from the Thau Lagoon, a shallow Mediterranean lagoon with frequent cyanobacterial blooms (89,90). The French Agence Nationale de Recherche has recently funded a three-year program to study the relationship between BMAA, cyanobacteria and ALS.

### Routes for human exposure to cyanotoxins

Cyanotoxins may enter the human body via oral, respiratory and dermal routes, including drinking water (which may be treated or raw), bathing, showering, swimming, water skiing, sailing, fishing, and haemodialysis (91). Aerosolization, which is a major route of exposure to marine red tide toxins (92), is also a potential exposure route for cyanotoxins (93). Consumption of fish, crustaceans and molluscs may be a major source of cyanobacterial BMAA, as well as food plants that have been exposed to BMAA (94) and dietary supplements made from cyanobacteria (91,95).

Fishermen, water treatment workers, those involved in fish farming and crop irrigation are potentially at risk of a high exposure to cyanobacteria. The reported increased incidence rates of ALS in deployed military personnel (20,22) might result from exposure to cyanobacteria, either from dust from desert cryptogamic crust (23,96) or from drinking or swimming in cyanobacteria-containing water.

### Lifetime exposure

Epidemiologic studies of Guam ALS suggested that the responsible environmental neurotoxicant(s) had very long incubation and wash-out times (97,98). Filipino immigrants to Guam did not develop the endemic high incidence of ALS for 10 + years after moving to the island and adopting the Chamorro way of life (97), while Chamorros who migrated to California developed ALS at a much higher frequency than the US population for 20 + years (98). Exposure to environmental factors in utero and the first few months of life may be important for the development of ALS many decades later; Ajdacic-Gross et al. (99) found that birth during spring months was a significant risk factor for ALS, and Sabel et al. (83) found that the place of birth was more important than subsequent places of residence.

### Geographical mapping of exposure risk to cyanobacteria

Caller et al. used Geographical Information Systems (GIS) mapping to demonstrate a 2.3-fold increased incidence of ALS within 0.5 miles of New Hampshire lakes with frequent cyanobacterial blooms (87,88). Costello et al. (100) found that residence within 500 feet of sources of high pesticide exposure increased the risk for Parkinson's disease by 75%. Sabel (83–85) developed novel spatial analytic techniques and found that the density of ALS cases in Finland was lower in urban areas and higher in adjacent rural regions that probably had more lakes and agricultural activities.

Epidemiologic research into an association between an environmental toxicant and place of residence or employment will need to determine GPS coordinates of those locations and relate them to proximity to a source of that toxicant, as well as the source(s) of the domestic water supply at those locations. In the case of cyanobacteria and BMAA, we hypothesize that the risk of developing ALS is highest close to water bodies subject to cyanobacterial blooms and highest where surface water and shallow wells provide the domestic water supply.

### BMAA or cyanobacteria in epidemiologic research into risk factors for ALS?

Studies of brain and other tissues of animals and humans referred to above have suggested an association between BMAA and ALS. Epidemiologic research offers a way of determining how strong a risk factor BMAA is for the development of ALS. Ideally, epidemiologic studies should determine an individual's cumulative dose of BMAA, the concentration of BMAA in the brain, and then relate these measures to the risk of developing ALS. There are several problems that make this difficult. First there

is currently no way to measure the BMAA content of living human brain. Secondly, the density of cyanobacterial populations in ecosystems varies greatly from time to time; in tropical latitudes blooms may be very long-lived, while in temperate latitudes populations may have great seasonal and spatial variability. Hence, spot sampling for cyanobacteria does not indicate the frequency or length of potential exposure. Thirdly, BMAA production by cyanobacteria is variable and influenced by factors that are not fully elucidated (37,38).

Thus, at present epidemiologic research into the association between BMAA and ALS and other neurodegenerative diseases cannot use direct measures of BMAA, and will have to rely upon exposure to cyanobacteria as a surrogate for BMAA exposure. There are several ways in which exposure to cyanobacteria may be estimated, including questionnaire, direct collection of environmental samples, hind-casting from studies of sediment cores and herbarium material, and in-lake and remote sensing technologies.

### Cyanobacteria exposure questionnaire

A widely applicable but indirect way to assess exposure to cyanotoxins is the use of a questionnaire that records the lifetime history of residences and places of employment and proximity to water bodies containing cyanobacteria. The GPS coordinates of those locations would be matched with databases of water bodies and cyanobacterial blooms (69,73–75,91,93, 101–107), and of the domestic water supply at those locations (108–110). The questionnaire would record the subject's lifetime history of the use of water bodies for recreation, and consumption of nutritional supplements derived from cyanobacteria (e.g. *Spirulina* or *Aphanizomenon*) (95). The cyanobacteria questionnaire could be added to the ACES modules (111), which are established and validated questionnaires to record demographic and other information of relevance to the risk of ALS.

### Methodologies to measure exposure to cyanobacteria

#### *Direct collection of environmental samples*

Specimens from the ecosystems to which an individual has been exposed may be used to quantify the concentration of cyanobacteria and BMAA using established sampling protocols (112). Samples may be whole water or filter collections from estimated volumes of water, (semi-)solid material like water body scums and shoreline biofilms, and dry samples like desert cryptogamic crust. However, these specimens provide only cross-sectional snapshots of the cyanotoxin contents of the ecosystem at the time of collection, while the relevant exposure may extend over decades. Longitudinal databases of

relevant ecosystems are needed, but at present such databases are limited both in coverage and detail. Some statewide projects are beginning to collect such data (107).

#### *Sediment studies*

Study of lake sediment cores can provide a record of the cyanobacterial blooms extending over decades (113,114). Push cores (~1 m long, 15 cm diameter) are sectioned at 0.5–2-cm intervals allowing analysis of the top (most recent) slice to the bottom (oldest) slice of the core. Each slice is dated by determining the ratio of  $^{137}\text{Cs}$  to  $^{210}\text{Pb}$  (115–117). The cyanobacterial load of the water body at the time of deposition of each slice is estimated by measuring the concentration of cyanobacterial paleo-pigments. However, sediment cores do not allow determination of the concentration of BMAA produced by the cyanobacteria at any point in time, and are best applied to lakes and lagoons because water movement may impair the historical record in rivers and seas.

#### *Herbarium specimens*

The cyanobacterial content of environmental samples from water bodies can be determined from historical material preserved for microscopy (112). Dried specimens of cyanobacteria from identified water bodies that were stored under herbarium conditions for at least a century have provided data on the past occurrence of cyanotoxins (118,119).

#### *Remote sensing and in-lake spectroscopy techniques*

Remote sensing techniques based on spectral patterns of light reflected from water bodies containing cyanobacterial blooms are available to detect and quantify large-scale cyanobacterial load in inland and coastal water bodies, and open seas (120–123). Although these methodologies are indirect and only measure cyanobacteria close to the surface, good correlations have been found between spectral reflection from cyanobacterial pigment phycocyanin and concentrations of microcystins (120,121). Remote sensing can be carried out from research aircraft (120) or satellites, and the latter may provide data from many passes over the same water body to provide a multi-year timeline of cyanobacterial content and distribution (124).

### Epidemiologic studies to determine the relative risk for ALS of exposure to cyanobacteria

The thesis of this paper is that epidemiologic studies should be used to estimate the relative risk for the development of ALS from exposure to cyanobacteria. Two approaches are possible:

studies of the incidence of ALS in regions with 'high', 'medium' and 'low' cyanobacterial loads; and retrospective studies of exposures to cyanobacteria in ALS patients and matched controls. Florida would be ideal for such studies because we have demonstrated in Florida that BMAA occurs in cyanobacteria in the ecosystem, crustaceans and other food sources, and human ALS brains (70,79,81). Florida has many lakes, rivers, canals, shallow estuaries and seas that are subject to increasingly frequent cyanobacterial blooms, and has a significant environmental contamination with mercury (125); mercury and BMAA are synergistic neurotoxins (126).

### Gene-environment interactions

It is highly likely that gene-environment interactions are relevant for all environmental causes of sALS. At the height of the ALS 'epidemic' on Guam in the decade after World War II, no more than 5% of the deaths of Chamorros on the island were due to ALS (39), even though it must be presumed that a large proportion of the population was exposed to BMAA. We hypothesize that, although the dose of BMAA that the Florida ALS patients had absorbed over years or decades may be an important risk factor for the development of ALS, there must be an additional susceptibility of sALS patients to BMAA compared to the control population. This increased susceptibility could result from genetic differences in absorption, distribution and metabolism of BMAA. In rodents, BMAA is transported across the blood-brain barrier by the L-1 large neutral amino acid transporter (127), and is misincorporated into brain proteins where it remains for prolonged periods (64). Human neuronal cell lines misincorporate BMAA into proteins via seryl-tRNA synthetase (65,66).

An increased susceptibility of ALS patients to BMAA could result from increased affinity of the neutral L-1 amino acid transporter for BMAA resulting in more BMAA crossing the blood-brain barrier and reaching the brain, or from decreased ability of the seryl-tRNA synthetase to distinguish BMAA from L-serine, allowing increased incorporation of BMAA into neuronal proteins. Alterations in the transporter and synthetase functions could result from mutations or polymorphisms of the genes for these proteins; a mutation of the alanyl-tRNA synthetase gene in the mouse allows misincorporation of serine in place of L-alanine, leading to a chronic cerebellar neurodegeneration (128). Mutations of several tRNA synthetases cause hereditary sensory-motor neuropathies (129,130).

A genome-wide association study (GWAS) of Guam ALS/PDC suggested an association with loci on chromosome 12 and 17 (131), although no candidate genes have yet been proposed. To date few

genes controlling BMAA metabolism are known. BMAA is almost certainly not the only environmental factor responsible for sALS. A positive association in GWAS studies of those cases of sALS that resulted from susceptibility to BMAA would likely be obscured by cases with normal BMAA gene function but genetic susceptibility to other environmental factors. A targeted search of genes involved in the metabolism of BMAA, such as the LAT1 and LAT2 genes for the L-1 amino acid transporter (132) and the SARS gene for seryl-tRNA synthetase (<http://omim.org/entry/607529>) would be interesting.

### Conclusions

The BMAA theory proposes that the environmental cyanobacterial toxicant, BMAA, is a risk factor for the development of ALS and other age-related neurodegenerative diseases in genetically vulnerable individuals. Epidemiologic research offers an opportunity to determine how large an etiologic role environmental exposure to BMAA plays in sALS. Study of lifelong exposures to environmental toxicants will be important in assessing the relative importance of each toxicant as a risk factor for ALS. Since it is currently not possible to determine an individual's lifetime cumulative exposure to BMAA per se, estimation of exposure to ecosystems containing cyanobacteria may be used as a surrogate for exposure to BMAA. Ways to provide semi-quantitative estimates of exposure to environmental cyanobacteria reviewed in this article include a suitably designed questionnaire, and direct and indirect measures of cyanobacterial content of ecosystems. Epidemiologic studies, including analysis of gene-environment interactions, will advance understanding of the role of BMAA and other environmental toxicants in ALS.

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