

Murky Water: Cyanobacteria, BMAA and ALS

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Abstract: Cyanobacteria have been implicated in the etiology of ALS for the past 50 years. The weakness of the theories of cyanobacteria or its neurotoxin, BMAA as the etiologic agent in ALS is the iniquitousness of cyanobacteria in the environment. In third world countries, clean water is far from commonplace, the exposure to cyanobacteria higher, yet the incidence of ALS is probably less than it is in developed countries. Even in the developed world, exposure to cyanobacteria is commonplace. Differences in the gut microbiome, possibly the presence of Proteobacteria, a protective agent against cyanobacteria toxins, may be important.

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Hypothesis

Exposure to Cyanobacteria and/or its toxin, BMAA is commonplace by adulthood in virtually all adults. The occurrence of ALS is a function of genetic susceptibility, changes due to aging and the possible alterations in the gut microbiome. Proteobacteria may be protective.

Introduction/Background

High incidence of amyotrophic lateral sclerosis (ALS) occurred among the Chamorro natives in Guam back in the 1940s and 1950s, leading scientists to link cyanobacteria and one of its neurotoxin, beta-N-methyl amino-L-alanine (BMAA) to ALS. Subsequent findings of the regular biosynthesis of BMAA in the Baltic Sea combined with its possible transfer and bioaccumulation within major food webs, some ending in human consumption, has been alarming [1]. A prevailing theory has been that long term, chronic exposure to low levels of BMAA through the environment, in areas with algae blooms, occurs through biomagnification which might cause ALS in genetically predisposed individuals. Recent studies from Scandinavia have been far less supportive, finding limited evidence for the theory among retail coastal seafood. BMAA was identified in blue mussel, oyster, shrimp, plaice, char and herring, but was undetectable in other samples (salmon, cod, perch and crayfish) casting doubt on biomagnification in many seafood networks humans eat [2]. Others are more skeptical of any cyanobacteria or BMAA connection and believe poor reporting and analysis and prolific errors have weakened the research [3]. Yet, research from plausible, rational studies showing a possible link have been published in credible journals.

Hypothesis/Theory

The unrecognized weakness of the cyanobacteria theory is the "dirty water" problem. Throughout most of time and now in many parts of the world, clean water hasn't existed. People drank water contaminated with many things, including cyanobacteria, for millennia. In

the clearest pool of water along the stream, the blue green algae lurks. Purified water is a recent development, along with the flush toilet. If chronic, low-grade exposure to cyanobacteria or one of its toxins, such as BMAA, were the principle factor leading to ALS, mankind would have had a very different evolutionary experience. Granted, in most primitive societies, most individuals don't live to their 60s. Even so, we would expect the frequency of affliction to have been much greater than is common now. Reported experiences would have shown ALS incidence to be higher than the US rate and very common in the third world, but it hasn't. Most investigators would be surprised to find the incidence rate even equivalent to the US.

BMAA, a neurotoxic, highly reactive nonessential amino acid, can be found either free or protein-bound. It is produced from members from all major cyanobacteria groups [4] and for this reason it is believed to be widespread in freshwater systems and habitats such as rivers, ponds, lakes, groundwater or even scum in fish tanks because cyanobacteria is commonly present. Many exposure routes to cyanobacteria have been implicated, including consumption of contaminated food and aerosolization of water harboring cyanobacteria that could produce BMAA [5]. Hence, it seems possible and plausible that all subjects who reach adulthood will have had exposure to cyanobacteria and the potential for temporary or minor gut colonization, with greater or prolonged colonization in susceptible individuals.

If cyanobacteria or cyanobacteria produced BMAA are important, then the difference must lie in our gut microbiome. No one expects the gut microbiome of Westerners to be identical to third world populations. For the millennia up to the twentieth century, those lacking the necessary complement of bacteria or immune system to either displace cyanobacteria or degrade its toxins, including BMAA, would be stricken. If that had been the experience, every primitive society would have been familiar with ALS and have their own name for the condition. Such is not the case.

The complex symbiotic inter-relationship between the GI-tract microbiome and its host is strongly influenced by diet and nutrition, impacting the microbiome composition and the metabolic activities of the microorganisms. Typical Western diets contain relatively large amounts of protein, fat and cholesterol, low amounts of soluble and insoluble fiber and relatively high amounts of sugar and salt than would be expected in more primitive societies or third world diets. In turn, this impacts the supply of substrates to the gut flora and the subsequent generated molecules that maybe absorbed into the systemic circulation. Some microbes are better suited to complement specific metabolic enzymes over others depending on nutritional substrates provided by diet. For example, *Bacteroides* change how they breakdown carbohydrates depending on if they received the right amount of certain substrates [6]. Similarly, in cultured environments cyanobacteria BMAA production is increased in a nitrogen depleted environment [7]. Thus, this provides some plausible rationale for the clinical observation of improved outcomes and recommendation for high protein diets in ALS patients.

The GI tract contains the largest reservoir of microbes in the human body. Of the 55 bacterial divisions currently identified, only two are prominent in mammalian GI-tract microbiome, the anaerobic *Bacteroidetes* (~48%) and *Firmicutes* (~51%), with the remaining phylotypes (~1-2%) distributed amongst *Actinobacteria*, *Proteobacteria*, and *Fusobacteria* with various species of fungi, protozoa, viruses, and other microorganisms making up the remainder (<1%) [8]. Not all the species in the gut have been identified because most cannot be grown [9],[10] and identification of specific organisms is difficult. Each individual has a uniquely proportioned composition of microorganisms in their gut -- a result of diet, exposure, immunology and genetics. Only a small number of species are shared by all individuals constituting the human intestinal microbiome phylogenetic core [11].

Hence, it would seem implausible that ALS is due to a deficiency in this common core of organisms because it affects just 1-2 per 100,000 in the US population with small variability depending on race and ethnicity. Gut populations of species vary widely among different individuals but stay fairly constant within an individual over time, even though some alterations may occur with changes in lifestyle, diet and age [12],[13]. Colonization history, exotic exposures through foreign travel and immune status may all contribute to flora content and constituent quantity [14]. In the face of age related increased bowel absorptive changes, reductions in absolute gut microbe numbers and possibly "beneficial" bacteria, previously tolerated chronic low levels of BMAA production by cyanobacteria colonization may become pathogenic [15]. Recent animal findings suggest that environmental factors maybe more important than genetic susceptibility in determining who manifests ALS.

In animal models, the "non-pathogenic" composition gut microbiome dramatically determines colonic permeability even in genetically identical immunocompetent animals [16],[17]. Furthermore, emerging evidence has implicated key changes in the intestinal homeostasis that may be playing a role in the pathogenesis of ALS. On a structural level, scientists have discovered damaged tight junctions and reduced expressions of tight junction protein ZO-1 and the adherens junction protein, E-cadherin, in the intestines of an ALS mouse mode [18]. These mice, who express mutant superoxide dismutase (SOD1), also demonstrated an increased number of abnormal Paneth cells, which specialize in secrete antimicrobial peptides including defensin 5 alpha. Of note were increased levels of IL-17, an inflammatory cytokine implicated in inflammatory bowel diseases. One can see how these changes could significantly alter the intestinal integrity and affect the microbiome of the gut. In fact, comparisons of the intestinal microbiomes of ALS patients with those of healthy patients showed significant differences in the ratios of bacteria in multiple genus, including a reduction

of beneficial microorganisms *Oscillibacter*, *Anaerostipes*, and *Lachnospiraceae* [19]. Conversely, harmful microorganisms including *Dorea* were found to be increased in ALS patients. Put together, these new findings provide further evidence of a link between the gut and the pathogenesis of the disease.

If cyanobacteria or BMAA are important in ALS and are present in the human gut microbiome, then presumably there exists one or more organisms that are protective. One such candidate is the *Proteobacteria*. Of the cyanotoxin degrading bacteria strains capable of degrading microcystin or carrying the *mIra* gene, a gene closely affiliated to known species or genera capable of degrading cyanotoxins, many predominantly belong to closely related members of the α -Proteobacteria. They also degrade other gut related resident *Cyanobacteria*-generated neurotoxins including saxitoxin and anatoxin-a which may further contribute to neurological disease [20]. If *Proteobacteria* are important protective organisms in the human gut microbiome then the recent glut of over the counter *Lactobacillus* supplements and probiotics treating a variety of GI complaints could fuel a rash of ALS in the future if *Proteobacteria* is displaced by *Lactobacillus* [21].

Fecal transplantation may offer a non-specific treatment of ALS without specifically knowing if *cyanobacteria* or BMAA is the etiologic agent or *Proteobacteria* is protective as long as the gut microbiome is important. Theoretically, by re-establishing homeostasis within the gut microbiome, the harmful effects of ALS maybe mediated, the disease stabilized or perhaps even reversed. An anecdotal report apparently exists but no data directly implicating the fecal microbiome in ALS, nor published case reports of fecal transplantation being successfully used in ALS patients were identified in a recent review [22].

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