Case Report

A Case Series of Potential Pediatric Cyanotoxin Exposures Associated with Harmful Algal Blooms in Northwest Ohio

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A Case Series of Potential Pediatric Cyanotoxin Exposures Associated with Harmful Algal Blooms in Northwest Ohio

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Abstract: Cyanobacterial harmful algal blooms (CyanoHABs) are increasing in prevalence and severity globally and locally in the Great Lakes region. CyanoHABs have the potential to produce serious adverse human health effects due to the production of cyanotoxins from cyanobacteria. Common routes of exposure include recreational exposure (swimming, skiing, and boating), ingestion, and aerosolization of contaminated water sources. Cyanotoxins have been shown to adversely affect several major organ systems contributing to hepatotoxicity, gastrointestinal distress, and pulmonary inflammation. We present three pediatric case-reports that coincided with CyanoHABs exposure with a focus on presentation of illness, diagnostic work-up, and treatment of CyanoHAB-related illnesses. Potential cyanotoxin exposure occurred while swimming in the Maumee River and Maumee State Park in Northwest OH during the Summer months which coincide with peak CyanoHAB activity. Primary symptoms included generalized macular rash, fever, vomiting, diarrhea, and severe respiratory distress. Significant labs included leukocytosis and elevated C-reactive protein. All patients ultimately recovered with supportive care. Symptoms following potential cyanotoxin exposure coincide with multiple disease states representing an urgent need to develop specific diagnostic tests of exposure.

Keywords: cyanoHAB exposure; pediatric case series; menstruation; macular rash; fever; vomiting; diarrhea; respiratory distress; leukocytosis

1. Introduction

Cyanobacteria are an ancient and widespread phylum of bacteria, found in nearly every environment on earth. Due to their color, they are often referred to as blue-green algae; while they are not algae, they are capable of photosynthesis, giving them a similar appearance to algae to the naked eye. Due to their photosynthetic nature, cyanobacteria produce chlorophyll a (but not b), which contributes to their strong green color. Overgrowths of cyanobacteria driven by eutrophication form Cyanobacterial harmful algal blooms (CyanoHABs) including the absolute and relative levels of nitrogen and phosphorus in run-off waters, which is heavily influenced by local agricultural and industrial practices[1].

During CyanoHAB events, the cyanobacteria begin producing a variety of toxins, including microcystins, saxitoxins, anatoxins, and cylindrospermopsins. These CyanoHAB events typically take place in the late summer months, when the waters are warmest, however several cyanobacteria strains (e.g. *Planktothrix, Aphanizomenon, and Anabaena/Dolichospermum*) are cold-resistant and thus capable of extending blooms into winter months and colder climates[2,3]. As CyanoHAB events become more complex and persistent (in some cases, year-round), the window of exposure may be increased and the number of toxins to which humans and animals may be exposed may increase as multiple cyanobacterial strains produce a variety of cyanotoxins[4,5]. This complexity can result in a

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wide range of health effects in exposed populations, highlighting the importance of comprehensive monitoring and management strategies.

The family of microcystin toxins is one of the most common cyanotoxins produced in CyanoHABs and includes over 300 congeners[6]. Of these congeners, microcystin-leucine-arginine (MC-LR) is one of the most common and toxic forms. Microcystins, and especially MC-LR, are potent hepatotoxins that enter cells through organic anionic transporting polypeptides (OATPs). Microcystins exert their toxic effects largely through their strong inhibition of the serine/threonine protein phosphatase 1 and 2A (PP1 and PP2A)[7]. PP1 and 2A control a huge number of cellular processes (including most steps of the cell cycle) and making up as much as 1% of a cell's total protein[8]. As previously stated, microcystins are known to have toxic effects within the liver, though many of the body's major organ systems can experience these effects due to the expression of key OATPs throughout the body.

Saxitoxin is a paralytical neurotoxin, which also acts as a precursor to several other paralytic shellfish toxins (PSTs). Saxitoxin and its family members function largely by inhibition of the voltage-gated sodium ion channel, though saxitoxin and some of its derivatives can also work to inhibit the potassium and calcium voltage-gated channels[9,10]. Anatoxins, sometimes referred to as the "very fast death factor," are another common form of cyanotoxin. These toxins work by binding to acetylcholine esterase in muscle cells, forcing sodium ion channels to remain open, which then induces uncontrollable muscle contraction. Cylindrospermopsin has a variety of health effects, including gastrointestinal complications, liver inflammation and hemorrhage, pneumonia, and dermatitis. These arise from cylindrospermopsin's inhibition of cytochrome P450 and glutathione-s-transferase[11].

The most common routes of exposure to cyanotoxins are oral/ingestions, inhalation, and dermal contact with contaminated water[12]. Of these, the most highly studied route of exposure is the ingestion of contaminated water or seafood, which can lead to intestinal illness as well as the typical hepatotoxic effects. However, recent studies have shown that cyanotoxins can be aerosolized into water droplets by natural wave motion, showing the need for more studies on the inhalation route of exposure[13,14]. Recently, there is evidence that aerosolized MC-LR induces inflammatory signaling in healthy airway epithelial cells and may increase neutrophilic migration to the airways[14]. Additionally, both epidemiological data and preliminary research indicates some dermatotoxic effects of cyanotoxins, which has been understudied to date[15,16].

Both the frequency and intensity of CyanoHABs have been increasing in recent years, affecting all 48 contiguous states in the U.S. and many countries around the world including New Zealand, China, South Africa, Canada, and Kenya, to name a few[17]. As CyanoHABs become more frequent, health care professionals must be cognizant of symptoms and various presentations of patients affected by cyanobacterium toxicity. Herein, we present a series of 3 pediatric cases that coincided with CyanoHAB exposure with a focus on presentation of illness, diagnostic work-up and treatment of CyanoHAB-related illnesses. All three cases occurred in the western basin of Lake Erie or in the river that supplies it, and occurred in 2014, 2015, and 2016. The CyanoHAB tracking and intensity data for each of these years in the western basin of Lake Erie is shown in Figure 1.

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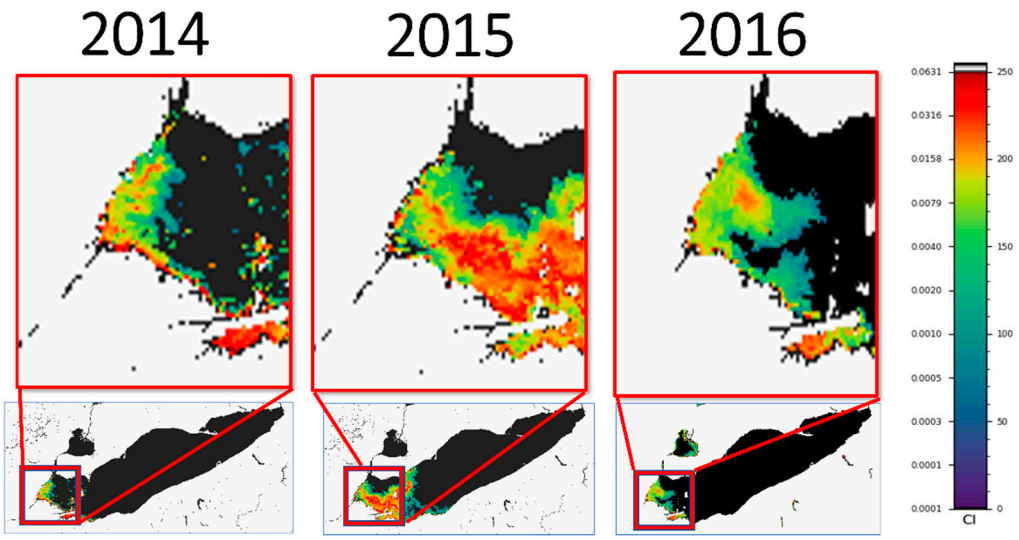

Figure 1. MODIS (Moderate resolution imaging spectro-radiometer) data of Lake Erie CyanoHAB intensity processed by NOAA National Centers for Coastal Ocean Science. Years of CyanoHAB monitoring presented correlate to the years of the cases presented below. Method described in Wynne and Stumpf, 2015[18]. Digital Number (DN) to Cyanobacterial Index value is CI = 10^(3/250*DN -4.2). Values of >0.001 (100 DN) is moderate risk, while >0.01 is high risk.

2. Case Report

2.1. Case 1

Case 1 (2016): 16-year-old female with no significant past medical history who presented with genital lesions, headache, generalized macular rash and fevers. Initially, she was treated as an outpatient for a yeast infection with fluconazole and an over the counter cream for vulval itching; however, due to fever and rash associated with worsening of symptoms she was hospitalized. Her CyanoHAB exposure occurred in June 2016, in the inlet of the Maumee river in Lucas County Ohio (Figure 1, Right column). This exposure was 2 weeks prior to admission, while symptoms started 1 week after the exposure. The patient's brother who also had been swimming in the CyanoHAB contaminated waters had similar symptoms that self-resolved. Of note, the patient was menstruating with tampon use during the exposure. Large CyanoHABs were reported in the area that the patient and her brother were swimming one day after exposure. In the hospital, the patient's labs were significant for thrombocytopenia, transaminitis, and mild leukopenia. Extensive work-up showed no specific etiology and together with her clinical findings and history of exposure, she was presumed to have toxic effects from CyanoHAB exposure and CyanoHAB toxins.

2.2. Case 2

Case 2 (2015): 14-year-old female, with past medical history significant for MRSA skin infection and depression, who presented with 2 days of fever, rash, vomiting, diarrhea, and dehydration. Her CyanoHAB exposure occurred while swimming in the Maumee Bay State Park, in July of 2015 (Figure 1, Middle column), which was reported to be 2 days prior to onset of fevers followed by vomiting and then diarrhea. She was also menstruating during exposure with tampon use during her swim in the lake immediately prior to the area closing for human activity due to increased CyanoHABs. Differential diagnosis on admission included toxic shock syndrome. Her laboratory studies in the hospital were significant for leukocytosis with increased bands, positive for toxic granules in neutrophils, elevated C-reactive protein, and mildly elevated creatinine. Patient was admitted to the pediatric intensive care unit, had a rapid recovery. Bacterial etiology was ruled out with negative

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cultures and given the history of CyanoHAB exposure, toxic effects from CyanoHAB toxins was presumed.

2.3. Case 3

Case 3 (2014): 7-year-old female with significant history of poorly controlled asthma presented with decreased responsiveness, tachycardia, diminished breath sounds and severe respiratory distress which required immediate intubation. Her symptoms started immediately after CyanoHAB exposure from swimming in the Maumee Bay State Park in July 2014 (Figure 1, Left column), and did not improve with albuterol treatments at home. Her chest x-ray showed multiple areas of atelectasis and right lower lobe infiltrate. Her labs were significant for leukocytosis, increased bands, and her overall hospital course was lengthy complicated by steroid-induced myopathy. The patient eventually made a full recovery. Based on persistent negative testing for viral or bacterial etiology along with history of CyanoHAB exposure the patient was diagnosed with presumed toxic effects from CyanoHAB toxins leading to acute respiratory failure.

Table 1. Patient characteristics summary.

Patient	Case #1	Case #2	Case #3
Age (yrs)	16	14	7
Sex	Female	Female	Female
CyanoHAB Exposure date	June 2016	July 2015	July 2014
PMHx	No significant PMHx	MRSA and depression	Asthma
Means of Exposure	Swimming (Maumee river)	Swimming (Maumee Bay State Park)	Swimming (Maumee Bay State Park)
Menstruation	Yes (with tampon)	Yes (with tampon)	No
Primary Symptoms on admission	Generalized macular rash, fever, headache, genital ulcers	Generalized macular rash, fever, vomiting, diarrhea, and dehydration	Listless, tachycardia, diminished breath sounds and severe respiratory distress
WBC (x1000 per μL)	3.6	22.5	15
Band (%)	N/A	26%	20%
Hemoglobin (g/dL)	13.2	13.3	12.2
Platelets (x1000 per μL)	94	247	467
AST (U/L)	192	32	24
ALT (U/L)	211	15	18
Creatinine (mg/dL)	0.84	1.29	0.39

[1] Case presentations coinciding with CyanoHAB events. PMHx, past medical history; WBC, white blood count; Band%, band neutrophil concentration; hemoglobin; Platelet, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

3. Discussion

Here, we present three pediatric patient cases with cyanotoxin exposure that aligned with documented CyanoHAB events in the Western Lake Erie Basin. The patients were females, between the ages of 7 and 16, presenting with symptoms such as: generalized macular rash, fever, vomiting, diarrhea, and severe respiratory distress, among others. All three were exposed to waters that were contaminated with cyanotoxin-producing bacteria around the same time as onset of symptoms. In each case, symptoms resolved with supportive care, and patients recovered quickly. Notably, two of the cases involved patients who were menstruating with tampon use. In one case, a biologically male relative had concurrent exposure, which resulted in mild symptoms that self-resolved, suggesting that menstruation status may play a role in cyanoHAB-related exposure and illness.

Currently the diagnosis of cyanotoxin exposure and related illness is a diagnosis of exclusion. The World Health Organization (WHO) is responsible for the creation and maintenance of the

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International Classification of Diseases (ICD) classification system to serve as a key method for identifying health trends and statistics globally and is the international standard for reporting mortality, morbidity and other conditions affecting health including diagnoses, symptoms and procedures recorded in conjunction with hospital care. The ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) in the United States contains specific codes for both "Contact with and (suspected) exposure to harmful algae and algae toxins" (ICD-10-CM Code Z77.121) and "Toxic effect harmful algae & algae toxins" (ICD-10-CM Code T65.82). Lack of awareness of both CyanoHABs-specific ICD codes and CyanoHABs in general, may lead to underreporting of exposure and toxicity events. The Centers for Disease Control and Prevention (CDC) recommends the use of these codes in diagnosing and recording CyanoHAB-related exposure and illnesses (Table 2).

CyanoHABs are a growing public health concern and key knowledge gaps in cyanotoxin research need to be addressed. Though the liver is a key target for cyanotoxins such as microcystin, work from our lab has shown that merely monitoring aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels may be insufficient for diagnosis, requiring other methods of detecting damage to organ systems such as the liver[19]. Additionally, work from our lab and others show that microcystin impacts the kidneys and gut, and may also work as a cardio-[20,21] and neurotoxin[22]. Beyond microcystin, other cyanotoxins (including saxitoxin, anatoxin, and cylindrospermopsin) affect a variety of organs and organ systems8. While microcystins in tissues can be detected using enzyme-linked immunosorbent assays (ELISA), protein phosphatase inhibition assays, and Lemieux oxidation, none of these methods are capable of differentiating between different congeners and metabolites of microcystin[23].

Our preliminary work indicates that high-resolution Mass Spectrometry (MS) and Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) imaging could be useful for closing some of these knowledge gap[23,24]. MS is a powerful tool that could potentially be used for the detection of some Cyanotoxins and their metabolites from patient samples[23,24]. This would both allow healthcare providers to diagnose what specific toxin(s) may be responsible for illness, as well as provide appropriate supportive care. Our lab has also helped develop techniques that reveal the spatial distribution of some cyanotoxins in tissue, and can even reliably detect the concentration gradient throughout a tissue section. While these are still in the early stages of development, they show promising results for the detection of microcystin from plasma, urine, as well as the presence and localization of microcystins in tissue [23–25]. Practical and reliable detection of cyanotoxins, along with pathologic thresholds, would be greatly assist diagnosis and targeted treatment of patients exposed to cyanotoxins.

The prevalence and persistence of CyanoHABs are increasing globally, raising the likelihood that more people will be at risk for cyanotoxin exposure and illness. Additionally, work from our lab has shown that several common comorbidities affecting the liver [19,26], gut[27], and airways[14] may increase susceptibility to cyanotoxins such as microcystin. As the incidence and prevalence of diseases such as non-alcoholic fatty liver disease, inflammatory bowel disease, and asthma increase, this may have profound impacts on the health of at-risk populations who are exposed to CyanoHABs.

Because specific diagnostic and therapeutic options for CyanoHAB related exposure and illness are lacking, we have an incomplete clinical picture of the extent of Thus it is important that healthcare providers and public health officials are vigilant in recording and tracking exposure events and related illness so that a more complete clinical picture of patient symptoms and outcomes can inform advancements in preventative, diagnostic and therapeutic strategies. Toward this end, Table 2 highlights several useful resources for Healthcare providers and public health officials for use in diagnosing and recording CyanoHAB-related exposure and illnesses as well as for education of the public about the health risks of CyanoHAB-related exposures.

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Table 2. CyanoHAB References for Healthcare and Poison Control professionals.

Agency	Resource
World Health Organization (WHO) International Classification of Diseases (ICD)	ICD-10-CM codes recommended by the Centers for Disease Control and Prevention (CDC) for use in diagnosing and recording CyanoHAB-related exposure and illnesses: **Z77.121:** Contact with and (suspected) exposure to harmful algae and algae toxins **T65.82:** Toxic effect harmful algae & algae toxins
Centers for Disease Control and Prevention (CDC)	Harmful Algal Bloom-Associated Illness Fact Sheets and Reference Cards (Physician Reference, Cyanobacteria FAQ, Facts about Cyanobacterial Blooms for Poison Center Professionals) https://www.cdc.gov/habs/materials/factsheets.html
One Health Harmful Algal Bloom Reporting System (OHHABS)	OHHABS Reporting Infosheet https://www.cdc.gov/habs/pdf/ohhabs-reporting-flow-diagram-508.pdf OHHABS Factsheet https://www.cdc.gov/habs/pdf/ohhabs-fact-sheet.pdf User Resources for the: One Health Harmful Algal Bloom System (OHHABS) and National Outbreak Reporting System (NORS) https://www.cdc.gov/habs/pdf/ohhabs-fact-sheet.pdf
Great Lakes HABs Collaborative	Harmful Algal Blooms and Human Health Effects https://www.glc.org/wp-content/uploads/HABS-FactSheet-Chronic-Health-202205.pdf Harmful Algal Bloom Toxins in the Air https://www.glc.org/wp-content/uploads/HABS-FactSheet-Toxins-in-Air-202205.pdf

[2] Harmful Algal Bloom references and resources for physicians and poison control professionals. Resources come from health and regulatory agencies: a) The Centers for Disease Control and Prevention, b) One Health Harmful Algal Bloom Reporting System (OHHABS), and c) Great Lakes HABs Collaborative.

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Data Availability Statement: All relevant data is available within Table 1.

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