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The association between razor clam consumption and memory in the CoASTAL cohort

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ABSTRACT

This study represents a preliminary effort to examine the potential impacts of chronic, low level domoic acid (DA) exposure on memory in the CoASTAL cohort over the first four years of data collection (Wave 1). Five hundred and thirteen adult men and women representing three Native American Tribes were studied annually with standard measures of cognition and razor clam consumption (a known vector of DA exposure) over a four-year period. In addition, a pilot metric of DA concentration exposure was used which took into consideration average DA concentration levels in source beaches, as well as the amount consumed. Based upon generalized estimating equations (GEE) analysis, controlling for age, sex, race, year, education level, tribe, and employment status, findings indicated that high razor clam consumers (15 or more per month) had isolated decrements on some measures of memory ($p = 0.02–0.03$), with other cognitive functions unaffected. The relatively lower memory scores were still within normal limits, and were thus not clinically significant. The pilot DA exposure metric had no association with any other aspect of cognition or behavior. There is a possible association between long-term, low-level exposure to DA through heavy razor clam consumption and memory functioning.

1. Introduction

The potential impact of domoic acid (DA) exposure to human health was discovered in 1987 in Montreal, Canada (Perl et al., 1990a,b; Teitelbaum, 1990; Teitelbaum et al., 1990). Many people who consumed affected mussels harvested from the Prince Edward Island (PEI) region suffered serious medical illnesses requiring hospitalization. Their symptoms included vomiting, abdominal cramps, diarrhea, headache, amnesia, seizures, coma and in some cases, death. Because of the memory problems observed in the majority of cases presented for medical treatment, comprehensive neuropsychological testing was performed on 14 survivors four months to one year after exposure and illness onset. Of the 14 people studied, one case had a completely normal neuropsychological profile and another had a generalized intellectual impairment which was so severe, it precluded reliable testing. The remaining 12 cases had varying degrees of memory loss and, in several well-publicized cases, a true amnesia was discovered within the context of otherwise intact cognitive abilities (Zatorre, 1990). Postmortem studies identified abnormalities in the hippocampus and related structures, including the dorsal medial thalamus, amygdala, nucleus accumbens, insula and sub-frontal cortex—all of which are associated with the memory system of the brain (Teitelbaum et al., 1990; Zola-Morgan and Squire, 1993). The remarkable memory disorder in many of the patients, combined with the postmortem results, led to use of the term “amnesic shellfish poisoning” (ASP) to describe the syndrome associated

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with DA neurotoxicity. However, numerous questions remain regarding those individuals with only gastrointestinal symptoms, younger people who did not seek medical treatment or did not have premorbid medical problems, and people with the least symptoms during the PEI outbreak (Teitelbaum, 1990; Teitelbaum et al., 1990).

Domoic acid was reported for the first time in the US in the late summer of 1991 when pelicans and cormorants were poisoned in Monterey Bay, California after feeding on anchovies contaminated with DA (Walz et al., 1994). Within the next few years, DA was detected in shellfish, including Dungeness crabs and razor clams, on the coasts of Washington and Oregon, (Wekell et al., 1994). After extensive studies, razor clams became known as the most significant vector for DA exposure in humans. This is because razor clams retain the toxin for up to one year in the natural environment, or several years after being processed, canned or frozen (Wekell et al., 1994). Because of aggressive monitoring in the state of Washington by the Washington State Department of Health, DA levels for high-risk beaches are well-documented. Accordingly, over the past decade, persistent low levels of DA in razor clams appeared to be the norm with concentrations rarely exceeding the regulatory guidance level of 20 ppm on select beaches. When DA levels approached 20 ppm, beaches were closed for harvesting razor clams which has been protective, with only 24 probable and 1 confirmed case of ASP reported in humans in 1991 (Trainer and Hardy, 2015).

Meanwhile, coastal residents, including Native American subsistence harvesters, as well as recreational harvesters, continue to enjoy razor clams, which may contain low levels of DA. Since DA is a known neurotoxin, the question is raised as to whether or not chronic low level exposure may have some impact on human health. Animal studies, including those of rodents and non-human primates, reported changes in behavior and hippocampal cell death following exposure to both high and low levels of DA (Scallet et al., 1993; Sobotka et al., 1996; Slikker et al., 1998; Doucette et al., 2004; Schwartz et al., 2014). These animal models alerted us to the possibility that people who consistently consume shellfish with low levels of DA may be at risk for some level of mild neurotoxicity. Since there is no biological test or established method to determine the amount of DA people have consumed in razor clams in the past 20 years, one can only rely on estimates from consumption surveys and harvest data. These estimates, at minimum, need to be based upon consumption risk (how many razor clams did the individual consume) and general source data from shellfish samples at relevant harvesting beaches (did they collect and eat razor clams from a beach with documented low levels of DA that week or month). This study was initiated to determine whether or not a plausible relationship may exist between long-term, low-level DA exposure via razor clam consumption and human health problems. The goals of the study were twofold: (1) to examine high-, low-, and non-razor clam consumers with respect to performance on memory tasks and (2) to determine the utility of a gross metric of possible DA exposure, i.e., the product of consumption (the average number of razor clams consumed per month that year) over time (the annual mean measured domoic concentration, in parts per million, in razor clams at the beaches from which the participant harvested clams).

2. Methods and materials

2.1. Participants

Participants included 513 adult men and women from the CoASTAL cohort (Wave 1) ages 18 years and older. The CoASTAL cohort represents a random sample of Native Americans from three Pacific NW tribes who, by virtue of their access to razor clam beaches and traditional diets, regularly consume razor clams (Fialkowski et al., 2010). The Wave 1 participants represent a cohort that was annually studied over a four year time period. Further details about recruitment methods and baseline data may be found in Tracy et al. (2016).

2.2. Measures

2.2.1. Demographic information

General demographic, developmental, academic, social, occupational, medical, neurologic, drug use, psychiatric, and exposure history were assessed using a modified version of the Boston Occupational and Environmental Neurological Health Questionnaire (Feldman, 1999). In light of the large amounts of fish and other seafood consumed by the CoASTAL cohort, this investigative team directly examined the possibility of methylmercury exposure. Based upon these studies, there were no elevated levels of methylmercury in this cohort that could potentially confound the cognitive findings (Tracy et al., 2016).

2.2.2. Cognitive assessment

Cognitive functions were assessed with standardized neuropsychological measures designed to evaluate memory within the context of other cognitive domains. The categories of cognitive functions assessed were: *simple and complex attention and concentration* [Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span (Wechsler, 1997); WAIS-III Digit Symbol Coding (Wechsler, 1997); Trail Making Test, Parts A and B (Reitan, 1992)], *constructional praxis* [WAIS-III Block Design (Wechsler, 1997)], *verbal memory* [California Verbal Learning Test-II Standard and short form (CVLT-II), (Delis et al., 2000)], *psychomotor speed and dexterity* [Lafayette Grooved Pegboard (Lafayette Instrument Company, 2002)], and *cognitive flexibility* [Trail Making Test, Part B (Reitan, 1992)]. Psychological functioning was assessed using standard measures of depression and anxiety including the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), respectively. Higher scores on each of these measures indicate more severe symptoms of depression and anxiety.

2.2.3. DA exposure

Razor clam consumption (as a potential marker for risk of DA exposure) was measured using the Shellfish Assessment Survey. This measure was previously validated by this research team for use in this regional, Native American population (Fialkowski et al., 2010). Participants were divided into non-consumer, high-consumer and low-consumer groups based upon the overall distribution of consumption scores. Individuals consuming 15 or more razor clams/month were considered high consumers and people who ate less were low consumers. Potential exposure to DA was also measured as the product of consumption (the average number of razor clams consumed per month that year) over time (the annual mean measured domoic concentration, in parts per million, in razor clams at the beaches from which the participant harvested clams).

2.3. Procedures

Written informed consent was obtained from all participants in compliance with standard procedures required by the University of Maryland Institutional Review Board. All measures were administered annually for four years by trained examiners in private field offices in the participants' communities. Exclusionary