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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 possible impacts of chronic, low level Domoic Acid (DA) exposure on memory in the CoASTAL cohort. Five hundred thirteen men and women representing three Native American Tribes were studied 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 consumption. Based upon 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 ($p=.02$ to $.03$), with other cognitive functions unaffected. The relatively lower memory scores were still within normal limits, thus not clinically significant. The pilot DA exposure metric had no association with any 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. The availability of a reliable biological marker for human exposure to DA is needed.

Keywords

Domoic Acid; Amnesic shellfish poisoning; environmental epidemiology; HAB illness; CoASTAL Cohort

Introduction

The potential impact of domoic acid exposure to human health was discovered in 1987 in Montreal, Canada (Perl et al., 1990a,b; Teitelbaum et al, 1990a,b). 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. Comprehensive neuropsychological testing was performed with 14 survivors four months to one year after the exposure and onset of acute illness. Findings indicated 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). Post mortem studies identified abnormalities in the hippocampus, an area of the brain associated with memory (Teitelbaum et al., 1990). The remarkable memory disorder in many of the patients, combined with the post-mortem results led to use of the term “Amnesic Shellfish Poisoning” (ASP), to describe the syndrome.

Domoic acid was reported for the first time in the US in late summer, 1991 when pelicans and cormorants were poisoned in Monterey Bay, California after feeding on anchovies contaminated with DA (Wekell et al., 1994). Within the next few years, DA was detected in shellfish throughout the Washington and Oregon coast including Dungeness crabs and razor clams. After extensive studies, razor clams became known as the most significant vector for domoic acid. This is because they 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, DA levels for high risk beaches are well documented. Accordingly, over the past decade, persistent low levels appeared to be the norm with occasional elevations in select regions. When DA levels approach 20 ppm, beaches are closed for harvesting razor clams and this has been protective with no cases of ASP reported.

Meanwhile, coastal residents 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 rodents and non-human primates reported changes in behavior as well as hippocampal cell death following exposure to both high and low levels of DA (Doucette et al., 2004; Scallet et al., 1993; Schwartz et al., 2014; Sobatka et al., 1996; Slicker et al., 1998) . These animal models alerted us to the possibility that people who consume shellfish with low levels of DA over time, 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 within the past 20 years, one can only rely on estimates. 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). To begin the process of determining whether or not a plausible relationship exists between long term, low level DA exposure, razor clam consumption and human health problems, this study was initiated. 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 (the average number of razor clams consumed per month that year) times (the mean measured domoic concentration, in parts per million, in razor clams at the beach(es) from which the participant ate clams that year).

Methods

Participants

Participants included 513 adult men and women from Wave 1 of the CoASTAL cohort ages 18 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. Further details about recruitment methods and baseline data may be found in Tracy et al., (in press).

Measures

Demographic Information and Potential Confounds—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 Health Questionnaire (Feldman, 1999). In light of the large amounts of fish and 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., in press). The Brief Michigan Alcohol Screening Test (BMAST) (Pokorny, Miller & Kaplan, 1972) and Alcohol Use Disorders Identification Test (AUDIT) (Babor, de la Fuente, Saunders & Grant, 1989) were used to screen for potential alcohol use problems.

Cognitive Assessment—Cognitive functions were assessed with standardized neuropsychological measures designed to assess memory within the context of other cognitive domains. The categories of cognitive functions assessed were: *simple and complex attention and concentration* [WAIS-III Digit Span, Digit Symbol (Wechsler, 1997); Trail Making Test, Parts A and B], *constructional praxis* [WAIS-III Block Design (Wechsler, 1997), *verbal memory* [CVLT-II Standard, Short Form (Delis, Kramer, Kaplan & Ober, 2000)]; *psychomotor speed and dexterity* [Lafayette Grooved Pegboard (Lafayette Instruments, Lafayette, IN 1989)] 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, Steer, & Brown, 1996) and the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1983), respectively.

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 (the average number of razor clams consumed per month that year) times (the mean measured domoic concentration, in parts per million, in razor clams at the beach(es) from which the participant ate clams that year).

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 by trained examiners in private offices at a field site in the participants' community. Exclusionary criteria included a history of severe dementia, severe head injury or other psychiatric or neurological disorder which precluded understanding informed consent or assessment procedures. The demographic, cognitive and shellfish consumption procedures took about 2.5 hours to complete and participants were reimbursed \$50 for completing all measures.

Data Analysis—Data were reviewed for completeness and distribution. Within each year, the analytic sample was categorized into three levels of consumption of razor clams: those who reported that they did not eat razor clams that year (non-consumers), those who reported eating fewer than 15 razor clams per month (low consumers), and those who reported eating at least 15 razor clams per month (high consumers). Responses for the fall/winter and spring/summer seasons within each year were averaged for each participant to produce their consumer category each year. In Year 1, the cut-off of 15 razor clams per month placed roughly twice as many participants into the low consumer group as into the high consumer group.

Bivariate analysis at Year 1 revealed differences in baseline characteristics between the no, low, and high consumer groups, using one-way analysis of variance and Pearson's chi-square tests. Data for all time points was considered in the analysis that sought associations between razor clam consumption and resulting scores on cognitive performance tests; this analysis used generalized estimating equations (GEE), to compare mean scores for each test between the three consumer groups, accounting for repeated measures within subject. Multivariable GEE models sought the same relationships, but were adjusted for age, sex, race (Native American or not), tribe, year, education level, and employment status. All GEE models were fit to a Gaussian distribution family and used the identity link function.

A final series of GEE models evaluated the associations between domoic acid exposure and scores on cognitive performance tests. Exposure to domoic acid was defined, in exposure units, in these models as the product of (the average number of razor clams consumed per month that year) times (the mean measured domoic concentration, in parts per million, in

razor clams at the beach(es) from which the participant ate clams that year). All coefficients for these GEE models were multiplied by 1000.

Relationships were considered statistically significant at $p = 0.05$. All data analysis was performed using STATA 12 (StataCorp, College Station, TX, USA).

Results

The sample included 513 adult participants who had sufficient data in Year 1 to be categorized into a consumer group (Table 1). The average age of the sample was 36.3 years old (standard deviation 12.4 years). More than half of the participants were low consumers in Year 1, and fewer than half were high consumers. One in five participants did not consume razor clams in Year 1. Majorities of the sample were females and unmarried. Approximately half of the sample reported current employment. Non-consumers of razor clams tended to be younger than low and high consumers.

Accounting for repeated measures but before adjustment for other covariates, consumption of razor clams showed few significant relationships with scores on cognitive performance tests (Table 2). High consumers had significantly lower T scores ($p=0.03$) and age-corrected scores ($p=0.05$) on the WAIS-III Digit Symbol Coding test (a timed task of sustained attention/concentration or clerical speed and accuracy). High consumers also had lower scores on the memory test: CVLT Trial 5 Free Recall ($p=0.03$) and CVLT Short Delay Free Recall ($p=0.02$) tests than did the non-consumers. The relationships between razor clam consumption and scores on the Beck Depression Inventory or the State-Trait Anxiety Inventory were not statistically significant in these models.

Adjusting for age, sex, race, tribe, year, education level, and employment status, high consumption of razor clams remained a significant predictor of lower scores on two of the CVLT memory recall tests (Table 3). Participants in the high exposure group, on average, scored 1.67 points lower on the CVLT Trial 5 Free Recall than did non-consumers ($p=0.04$) and 1.40 points lower on the CVLT Short Delay Free Recall ($p=0.05$). Consumption was negatively correlated with scores on the Beck Depression Inventory in these multivariable models, with low consumers scoring 1.10 points lower ($p=0.04$) and high consumers scoring 1.32 points lower ($p=0.05$) on average than non-consumers. When mean DA measurements at specific beaches were included as the exposure variable, DA exposure did not significantly predict any of the cognitive outcomes.

Discussion

This is the first cohort study to assess whether or not chronic, low level exposure to DA via razor clam consumption has a potential impact on human health. In this preliminary study, well validated measures of cognition and dietary consumption were employed to assess memory and razor clam consumption as an important first step toward identifying exposure risk (Tracy et al., in press). Findings suggest that very high razor clam consumers (greater than 15 clams/month) perform worse on memory measures than a reference group of non-consumers or low consumers. These findings could not be otherwise explained by age, sex, race, educational level, tribe, or employment status. Since a greater number of

depression symptoms were also associated with higher levels of razor clam consumption, consideration was given to its possible influence upon memory. However, the number of depression symptoms were at worst, within normal limits (i.e. not elevated enough to even consider a mild level of depression) and would not impact cognition. The isolated memory decrements, within the context of otherwise stable cognition in other domains, is consistent with the cognitive profiles of DA exposure in the index PEI exposure cases, although in attenuated form (Zatorre et al., 1990).

The pilot DA exposure measure that was used (average DA measurements from specific beaches X number of clams consumed) did not predict any of the cognitive outcomes. It is possible that the memory decrements in high consumers reflected DA exposures that predated the start of this study, when DA levels were significantly higher. Alternatively, the DA concentration exposure measure may have lacked sensitivity to exposure because it assumed DA levels at the beaches were fairly constant in razor clams in time and space. This is generally not the case as there can be variability in DA concentrations among razor clams from the same beach (Wekell et al., 2002). Moreover, DA levels can quickly and unpredictably fluctuate over time. Alternatively, it is possible that despite controlling for potential confounds, DA exposure level was not related to the memory findings. The final arbiter of this interpretation will be more advanced methods of assessing and modeling DA exposure.

An important caveat is whether or not the difference in memory performance among razor clam consumers has any clinical significance or practical significance on a daily basis. Despite the fact that the high consumer group had lower memory scores, the group as a whole still performed within normal limits on the memory measures. Further studies are underway to determine the functional impact of possible DA related memory inefficiencies in this cohort and examine subgroups within the high consumers. Meanwhile, the high consumers will continue to be followed closely over time as part of the larger CoASTAL cohort study. Finally, in the interest of protecting human health, after consultation with tribe leaders, participant communities have been advised to consider consuming fewer than 15 razor clams/month.

This study of the CoASTAL cohort highlights the importance of monitoring the cognitive functions of people at risk of DA poisoning. Additional studies are underway using alternate exposure metrics, more accurate “real-time” data collection about sourcing and consuming clams through cell phone technology (see Boushey et al., in press) and focusing on children and geriatric subgroups of the CoASTAL cohort. A priority for future research should be the identification and development of biomarkers for DA exposure.

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Table 1

Characteristics of adult and geriatric participants, by razor clam consumer group, at Year 1

	n with data	Full sample	Consumer group			P value ^x
			None	Low	High	
Number	513		20% (101)	53% (270)	28% (142)	
Age, mean± SD	509	36.3±12.4	32.2±11.5	37.1±12.9	37.6±11.3	<0.01 ^a
Gender, % Female (n)	509	59% (300)	69% (69)	57% (153)	55% (78)	0.07
Marital Status, % Married (n)	487	31% (151)	26% (25)	34% (86)	29% (40)	0.36
Employed, % (n)	504	51% (258)	52% (52)	50%	53% (75)	0.80
Educational level, % (n)	379					0.26
< High school (<12yr)		16% (59)	16% (13)	13% (25)	20% (21)	
High school (12yrs)		41% (157)	48% (39)	42% (82)	35% (36)	
13 or more years of school completed		43% (163)	37% (30)	45% (86)	45% (47)	

^x p values from Pearson's chi-square test, except

^a one-way ANOVA

Razor clam consumption groups were averaged and combined over fall/winter and spring/summer:

- None: Did not consume razor clams that year
- Low: Consumed fewer than 15 razor clams per month
- High: Consumed at least 15 razor clams per month

Cognitive data for performance on neuropsychological screening battery, by razor clam consumer group (n=513 participants with 1502 observations)

Table 2

	All groups			Consumer group		
	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	Low	High	
WAIS-III Digit Symbol Coding, n observations	1499	484	691		324	
T score	46.8 $\pm$ 9.4	47.2 $\pm$ 9.6	47.3 $\pm$ 9.5	0.41	45.1 $\pm$ 8.8	0.03
Age-corrected	9.1 $\pm$ 2.8	9.2 $\pm$ 2.9	9.2 $\pm$ 2.9	0.42	8.6 $\pm$ 2.6	0.05
WAIS-III Block Design, n	1490	479	689		322	
T score	48.2 $\pm$ 8.9	48.7 $\pm$ 9.3	48.5 $\pm$ 9.0	0.88	46.9 $\pm$ 8.3	0.17
Age-corrected	9.5 $\pm$ 2.7	9.7 $\pm$ 2.8	9.6 $\pm$ 2.7	0.90	9.1 $\pm$ 2.5	0.22
WAIS-III Digit Span, n	1494	480	690		324	
T score	45.6 $\pm$ 7.2	46.0 $\pm$ 7.6	45.6 $\pm$ 7.1	0.68	44.9 $\pm$ 6.7	0.73
Age-corrected	8.7 $\pm$ 2.2	8.9 $\pm$ 2.3	8.7 $\pm$ 2.1	0.83	8.6 $\pm$ 2.0	0.98
CVLT Trial 5 Free Recall, n	1494	484	689		321	
T score	41.0 $\pm$ 10.8	42.4 $\pm$ 11.1	40.5 $\pm$ 10.6	0.36	40.0 $\pm$	0.03
CVLT Short Delay Free Recall, n	1491	484	686		321	
T score	43.8 $\pm$ 10.7	45.4 $\pm$ 11.0	43.4 $\pm$ 10.6	0.51	42.1 $\pm$ 10.2	0.02
CVLT Long Delay Free Recall, n	1492	483	687		322	
T score	43.0 $\pm$ 11.4	44.5 $\pm$ 11.9	42.7 $\pm$ 11.0	0.74	41.7 $\pm$ 10.9	0.17
Trailmaking Test: Part A, n	1502	484	694		324	
T score	50.0 $\pm$ 10.1	49.5 $\pm$ 10.3	50.2 $\pm$ 10.4	0.81	50.2 $\pm$ 9.3	0.89
Trailmaking Test: Part B, n	1438	471	658		309	
T score	49.1 $\pm$ 9.5	49.5 $\pm$ 10.1	48.9 $\pm$ 9.4	0.34	49.3 $\pm$ 8.5	0.85
Laf. Grooved Pegboard, Dom. Hand, n	1476	482	678		316	
T Score	41.0 $\pm$ 11.2	42.0 $\pm$ 11.1	41.1 $\pm$ 11.3	0.56	39.2 $\pm$ 10.8	0.14
Laf. Grooved Pegboard, Non-dom. Hand, n	1460	478	671		311	
T Score	41.5 $\pm$ 10.3	41.9 $\pm$ 9.8	41.6 $\pm$ 10.8	0.99	40.6 $\pm$ 9.8	0.66
Beck Depression Inventory-II, n	1494	483	688		323	
Raw score	10.1 $\pm$ 9.5	10.6 $\pm$	9.9 $\pm$ 9.3	0.13	9.7 $\pm$ 9.2	0.27
State Trait Anxiety Inventory, n	1494	482	688		324	

	Consumer group							
	All groups		No		Low		High	
	mean ± SD	p value ^g	mean ± SD	p value ^g	mean ± SD	p value ^g	mean ± SD	p value ^g
State: Age-corrected	50.4 ± 10.2	49.7 ± 10.3	50.5 ± 10.1	51.2 ± 10.4	0.90	51.2 ± 10.4	0.97	
Trait: Age-corrected	52.4 ± 11.5	52.0 ± 11.7	52.5 ± 11.2	52.5 ± 12.0	0.88	52.5 ± 12.0	0.99	

^gGeneralized estimating equations for differences in score, comparing low or high consumer group to the non-consumer group, accounting for repeated measures and year. Models represented in this table are not adjusted for other covariates.

Razor clam consumption groups were averaged and combined over fall/winter and spring/summer:

- None: Did not consume razor clams that year
- Low: Consumed fewer than 15 razor clams per month
- High: Consumed at least 15 razor clams per month

Adjusted associations between seafood consumption and performance on neuropsychological screening battery(n=513 participants with 1502 observations).

Table 3

	Consumer Group				Avg. Razor Clam DA Exposure	
	None	Low	High		Coef. ^k	p-value ^g
WAIS-III Digit Symbol Coding	Coef.	Coef.	Coef.	p-value ^g		
Age-corrected Ref.	-0.10	0.46	-0.29	0.08	-0.47	0.27
WAIS-III Block Design						
Age-corrected Ref.	+0.07	0.61	-0.21	0.22	-0.47	0.30
WAIS-III Digit Span						
Age-corrected Ref.	-0.05	0.67	-0.11	0.49	-0.13	0.74
CVLT Trial 5 Free Recall						
T score Ref.	-0.57	0.38	-1.67	0.04	-2.28	0.28
CVLT Short Delay Free Recall						
T score Ref.	-0.50	0.38	-1.40	0.05	-1.56	0.41
CVLT Long Delay Free Recall						
T score Ref.	-0.10	0.87	-0.65	0.41	-2.61	0.20
Trailmaking Test: Part A						
T score Ref.	+0.09	0.89	-0.18	0.82	-1.15	0.59
Trailmaking Test: Part B						
T score Ref.	-0.45	0.44	+0.24	0.75	+1.65	0.39
Laf. Grooved Pegboard, Dom. Hand						
T Score Ref.	+0.05	0.94	-1.13	0.18	-3.96	0.08
Laf. Grooved Pegboard, Non-dom. Hand						
T Score Ref.	+0.20	0.75	-0.21	0.79	-0.11	0.96
Beck Depression Inventory-II						
Raw score Ref.	-1.10	0.04	-1.32	0.05	-1.48	0.41
State Trait Anxiety Inventory						
State: Age-corrected Ref.	-0.75	0.26	-0.99	0.23	-1.70	0.44
Trait: Age-corrected Ref.	-0.80	0.24	-1.39	0.10	-3.30	0.14

Adjusted for age, sex, race (Native American or not), tribe, year, education level, and employment status.

β Generalized estimating equations, accounting for repeated measures.

γ Coefficients for "number of razor clams consumed per month," are multiplied by one thousand.

Razor clam consumption groups were averaged over fall/winter and spring/summer:

- None: Did not consume razor clams that year
- Low: Consumed fewer than 15 razor clams per month
- High: Consumed at least 15 razor clams per month

Razor clam Domoic Acid exposure: Calculated as: (average number of razor clams consumed per month) time (average concentration, in parts per million, of Domoic Acid in razor clams at the beach(es) from which the participant ate clams that year.)