Residential and Recreational Acquisition of Possible Estuary-Associated Syndrome: A New Approach to Successful Diagnosis and Treatment

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Evidence suggests that the estuarine dinoflagellates, *Pfiesteria piscicida* Steidinger & Burkholder and *P. shumwayae* Glasgow & Burkholder, members of the toxic *Pfiesteria* complex (TPC), have been the primary suspects for causing multiple fish kills in North Carolina and other areas on the east coast of the United States (1–4). Recent evidence implicated the TPC as a possible human health risk factor. Exposure to air above fish tanks containing *P. piscicida* activated to kill fish in the laboratory was followed by a debilitating multisystem syndrome involving neurological, respiratory, and gastrointestinal dysfunction in several researchers, which persisted for months to years (5). A definitive association between TPC toxin(s) exposure and human illness has not been possible because of the lack of identification of, and blood tests for, the putative toxin(s) (6).

Initial evidence suggesting a potential human health risk from environmental exposure to TPC toxin(s) came from clinical examinations of patients, previously well, who became ill within hours of contact with the Pocomoke River and nearby Maryland estuaries around the time of fish kills attributed to TPC in 1997 (7). Reports by patients of symptoms similar to those reported by the researchers (5), including memory loss, confusion, decreased assimilation of new knowledge, headache, skin rash, burning skin upon contact with estuarine water, eye irritation, sensitivity to bright light, acute respiratory distress, diarrhea, and abdominal cramping led to a single-blind, case–control, clinical investigation (6). The estuarine cohort (i.e., potentially exposed) showed significant deficits relative to unexposed matched-control study participants in neuropsychological tests of verbal learning and memory, resistance to interference and selective attention, and motor speed and dexterity, when assessed within 2 weeks of estuarine contact. The test results also showed significant linear trends with worse performance in the more highly exposed estuarine-cohort participants (i.e., more time spent in TPC-inhabited estuaries). Performance among the most severely affected participants returned to within normal limits in 3–6 months following estuarine contact, although the completeness of recovery and possible effects of ancillary treatments were underestimated (8). Learning or attention deficits have also been observed in rodents injected with water from tanks in which TPC had been activated to kill fish (9–11).

The syndrome observed in the Maryland study participants was eventually termed possible estuary-associated syndrome (PEAS) by the researchers at Centers for Disease Control and Prevention (CDC) (12). The CDC case definition of PEAS consists of three components: a) exposure potential—symptoms reported within 2 weeks of exposure to estuarine waters; b) symptoms—memory loss or confusion of any duration and/or three or more selected symptoms (i.e., headache, skin rash at the site of water contact, sensation of burning skin, eye irritation, upper respiratory irritation, muscle cramps, gastrointestinal symptoms) that, with the exception of skin rash and burning skin sensation, persist for >2 weeks; and c) absence of confounders—a healthcare provider cannot identify another cause of the symptoms.

Because of concern about the potential for persistent, adverse health effects from contact with TPC-inhabited estuaries, a study was conducted by the State of North Carolina with assistance from the U.S. Environmental Protection Agency (U.S. EPA) and several local universities late in 1997 (13). The single blind, case–control, clinical investigation examined potentially exposed (i.e., estuary) watermen with no recent exposure to fish kills (i.e., 4 months or more since last contact) and unexposed (i.e., offshore) watermen. No significant group difference were observed in standardized medical, dermatologic, and neurologic examinations, a standard multiphasic biochemical/hematologic panel, and batteries of neuropsychological, neurobehavioral, and visual function tests. Only one test of visual
function consistently showed significant differences between the cohorts. The ability to detect visual patterns, as assessed by measurements of visual contrast sensitivity (VCS) (14–16), was reduced by about 30% in the estuary cohort (17). The cohorts did not differ in measures of visual acuity, suggesting that the VCS deficit was of neurological rather than optical origin. Further analyses of data from questionnaires indicated that the group difference in VCS was not likely due to potential group differences in age, smoking, alcohol consumption, bright sunlight exposure, or occupational exposures to mercury, lead, other metals, pesticides, fumes, solvents, or years of solvent exposure. Furthermore, the magnitude of the VCS deficit increased with increasing hours of long-past contact with fish kills (17). A similar group difference in VCS was subsequently observed in a Virginia study (18). In that study, VCS was significantly lower in an occupational and recreational cohort whose members spent time in estuaries where Pfiesteria-like organisms were present in ≥50% of samples than in a similar cohort in which the members spent time in estuaries where Pfiesteria-like organisms were present in only 19–36% of samples (18). These results suggested that the VCS test might provide an objective end point for detecting chronic neurological dysfunction associated with TPC-inhabited estuary contact.

A report on nonoccupationally related, acute, and chronic PEAS cases diagnosed at a private medical clinic in Pocomoke City, Maryland, indicated that a VCS deficit was present in subjects with either conditions (19). The VCS deficit greatest at midspatial frequencies (i.e., midsize dark and light bar sinusoidal gratings) was similar to but larger than that observed in the North Carolina estuarine cohort (13,17). Treatment with the toxin-binding polymer cholestyramine (CSM) (20) to increase toxin(s) elimination rate led to symptom abatement and VCS recovery in all cases within 2 weeks of treatment initiation (19). Cases with repeated acquisition of PEAS showed VCS loss, followed by recovery with CSM treatment on each occasion (19). Therefore, in addition to being a sensitive and objective indicator of both acute and chronic PEAS, VCS may be a useful tool for monitoring recovery during treatment.

The current study was undertaken to investigate the potential for unrecognized morbidity in a nonoccupational population that resided by or engaged in recreation in TPC-inhabited estuaries, but that did not have direct contact with fish kills or lesioned fish. Patients seeking medical attention at the Pocomoke City clinic during 1998 and 1999 for reasons not specifically related to estuarine exposure were informed about the study. The study was an assessment of a new method for detecting an environmentally acquired, chronic, neurotoxin-mediated illness without specifying estuaries or TPC. Following screening and exclusion for possibly confounding conditions and direct contact with fish kills or lesioned fish, patients who volunteered for study participation were categorized into one of three groups on the basis of responses to a demographics questionnaire: a) residential and/or recreational exposure to local, known TPC-inhabited estuaries (estuary cohort, potentially exposed); b) residential and/or recreational exposure to marine waters but not to TPC-inhabited estuaries (marine cohort, potentially unexposed); and c) no residential and/or recreational exposure to any body of water (land cohort, potentially unexposed). Visual acuity and VCS were measured in all study participants, and a questionnaire on current symptoms was administered at enrollment. Members of the estuary cohort were evaluated for PEAS. Participants meeting the case definition for PEAS underwent clinical and laboratory tests to identify other possible causes of their illness. The results suggested that there might be an unrecognized association in the estuarine population between morbidity and residential and/or recreational exposure to TPC-inhabited estuaries. The association apparently was due to a medical condition meeting the CDC case definition for PEAS in a subset of the estuary cohort.

Methods

Patients seeking medical attention at the Pocomoke City clinic were informed of a study on the use of VCS as a new tool for assisting the diagnosis of toxicity, without specifying a toxin source or a geographical area of risk. Patients who volunteered to participate in the study, with the consent of a guardian in the case of minors, were screened for potentially confounding factors and excluded from participation if they had serious ongoing illness requiring immediate medical care; a history of occupational exposure to solvents, metal fumes, petroleum products, and organochlorine pesticides; or previous diagnoses of a PEAS-like illness, a clinical diagnosis of alcoholism, Lyme disease, chronic ciguatera (fish) poisoning syndrome, possible building-related illness, or chronic soft-tissue injury. All patients enrolled were alert and oriented, without ongoing neurologic diagnoses.

Qualified volunteers were assigned to one of three groups designated for purposes of the study: a) estuary cohort (n = 77, age range = 22–73 years of age plus five children 5–14 years of age, 48 males and 29 females, average age = 44.8 ± 1.86 SEM, average years of education = 13.5 ± 0.4 SEM), residential and/or recreational, but not occupational, exposure to local rivers; b) marine cohort (n = 34, age range = 23–78 years of age, 23 males and 11 females, average age = 49.3 ± 2.8 SEM, average years of education 14.9 ± 0.4 SEM), occupational and/or recreational, but not occupational, exposure to ocean waters; and c) land cohort (n = 53, age range = 24–71 years of age, 26 males and 27 females, average age = 42.9 ± 1.5 SEM, average years of education = 14.6 ± 0.4 SEM), no exposure to any bodies of water. Symptoms were recorded using the classifications in Table 1, and visual acuity and VCS were measured in all patients immediately after enrollment in the study.

After the recording of symptomatic and visual function data, each estuary cohort member was questioned and examined to determine if he or she qualified for a diagnosis of PEAS according to the CDC criteria listed above. A general medical examination, complete blood count, comprehensive metabolic profile, and pulmonary function tests were administered to further identify potentially confounding conditions. The PEAS case definition was met by 37 of the 77 members of the estuary cohort. These cases were treated with CSM for 2 weeks according to a standard protocol. CSM (Questar; MFR Apothecon, Bristol Myers Squibb, New Brunswick, NJ, USA), one scoop, 9 g, was given, mixed well with water or apple juice, on an empty stomach, 30 min before eating or taking other medication, 4 times a day for 2 weeks (U.S. Food and Drug Administration (FDA))

Table 1. Symptoms in the Chesapeake Bay estuaries study on PEAS.

| Symptom             | Memory | Confusion | Headache | Skin rash | Burning skin | Eye irritation | Upper respiratory | Muscle cramping | Concentration | Light sensitive | Short of breath | Fatigue | Musculoskeletal | Abdominal pain | Vomiting |
|---------------------|--------|-----------|----------|-----------|-------------|---------------|-------------------|----------------|---------------|----------------|----------------|---------|----------------|----------------|---------|
| Cases (n = 37)      |        |           |          |           |             |               |                   |                |               |                |               |         |                |                |         |
| % Before Rx         | 84     | 73        | 16       | 8         | 68          | 41             | 14                | 57             | 35            | 68             | 43              | 57      | 43             | 35             | 41      | 16           |
| % After Rx          | 14     | 3         | 8        | 0         | 0           | 0              | 0                 | 5              | 3             | 5              | 0               | 24      | 5              | 5              | 14      | 0            |
| Noncases (n = 127)  |        |           |          |           |             |               |                   |                |               |                |               |         |                |                |         |
| % Before Rx         | 2      | 0         | 4        | 0         | 0           | 0              | 0                 | 0              | 1             | 0              | 2               | 2       | 3              | 0              | 2       | 2            |
| % After Rx          | 2      | 0         | 2        | 0         | 0           | 0              | 0                 | 0              | 1             | 3              | 2               | 2       | 1              | 0              | 2       | 1            |
exemption letter issued 6/28/99); the dose of CSM used is approved for treatment of hypercholesterolemia by the FDA. Sorbitol, 70% solution, 15 cc was also given, 3 times a day, as needed to relieve constipation, as was Prilocsec (Astra Merck, Wayne, PA, USA) or Prilocid (TAP Pharmaceuticals, Lake Forest, IL, USA) one capsule daily, as needed to treat reflux. Symptoms and VCS were reassessed immediately following treatment.

Three control studies were conducted before the study began to determine the variability in VCS measurements over time and CSM treatment efficacy. First, visual acuity and VCS were measured in 15 healthy adult volunteers at the beginning and end of a 2-week interval to assess potential effects of repeated VCS testing. Second, visual acuity and VCS were measured in 8 adult hypercholesterolemic volunteers before and after 2 weeks of CSM treatment to again investigate effects of repeated VCS testing and to assess treatment effects on VCS in a population with no known neurotoxicant exposures. Third, explicit informed consent was obtained from eight patients newly diagnosed with PEAS who had exposure to a fish kill or to fish with PTP lesions and who volunteered to participate in a clinical trial on the efficacy of CSM treatment on the VCS deficit and symptoms associated with PEAS. A double-blind, placebo-controlled, cross-over study design was used; we randomly assigned patients to the CSM treatment or placebo group. After 2 weeks in the first group, patients were switched to the opposite group for 2 weeks. VCS and visual acuity were measured and symptoms were recorded when diagnosis was made and when the patient completed CSM and placebo treatments. Neither the patient nor the investigator knew when the patient was in the CSM group or the placebo group. A study assistant nurse who made the group assignments also supplied each patient with packets containing either single doses of CSM or placebo powder (Tang; Kraft Foods, Northfield, IL, USA). Patients dissolved both powders in liquid, according to the protocol.

Vision Tests and Analyses

All subjects who normally wore corrective lenses for near-point viewing were asked to wear them during vision testing. The visual acuity and VCS tests were administered monocularly to each eye; an eye occluder was held over one eye while the other eye was tested. All vision tests were administered under illumination from a “daylight” illuminator (fluorescent source with a correlated color temperature of approximately 6500° K; color rendering index >90; intensity = 1150 lux; luminance, approximately 70 foot-lamberts) in a clinical unit that had normal background lighting. A light meter was used to ensure that luminance remained constant throughout the test sessions. A test card holder consisting of a face test placed just under the cheekbones or chin as comfort connected by a calibrated rod to a card holder on the distal end was used to position the acuity and VCS test cards at a constant distance, previously standardized, from the eyes [acuity, 36 cm (14 inches); contrast sensitivity, 46 cm (18 inches)].

Near visual acuity. The acuity test card (MIS Pocket Vision Guide, MIS, Inc.) contained 10 rows of numbers in which the size of the numbers progressed from larger in the top row to smaller in the bottom row. Participants were asked to first read the numbers in a middle row. Testing proceeded to the next lower row if all numbers were correctly identified or to the next higher row if an error occurred. The Snellen visual acuity of the row (20:20 or 20:30, for example) with the smallest numbers that were all correctly identified was recorded as the visual acuity score. Two-tailed Student’s t-tests with an α = 0.05 were performed, using the mean score of each participant’s two eyes, to determine if scores differed significantly between cohorts.

Contrast sensitivity. The contrast sensitivity test card (Functional Acuity Contrast Test, F.A.C.T. 101; Stereo Optical Co., Chicago, IL, USA) contained a matrix (5 × 9) of circles filled with sinusoidal gratings (dark and light bars). Spatial frequency (1.5, 3, 6, 12, and 18 cycles/degree of visual arc) increased from top to bottom, and contrast decreased from left to right in steps of approximately 0.15 log units. The grating bars were oriented either vertically or tilted 15 degrees to the left or right. As the investigator called out each circle from left to right, row by row, subjects responded by saying either vertical, left, right, or blank. Participants were encouraged to name an orientation if they had any indication that the bars could be seen. Participants (primarily the younger children) were asked to point in the direction to which the top of the grating was tilted if they felt any difficulty in verbalizing the orientation. The contrast sensitivity score for each row (spatial frequency) was recorded as the contrast of the last test patch correctly identified on that row following verification by repeated testing of that patch and the subsequent patch. The procedure was repeated for each row in descending order.

The a priori criterion for the inclusion of data in analyses was that the eye have a visual acuity (Snellen Distance Equivalent Score) of 20:50 or better to avoid confounding of the VCS results by excessive optical-refraction error. All eyes met the visual acuity criterion for inclusion in the data analyses.

Data analysis. The units of analysis for the VCS test were the mean scores of the participant’s two eyes at each spatial frequency. The VCS data were analyzed using multivariate analyses of variance (MANOVA, with the Wilks’ lambda statistic) procedures suitable for repeated measures with an α = 0.05. The factors in the model were group, spatial frequency, age, and their interaction terms. A factor for gender was not included, as no gender differences in susceptibility to TPC-induced effects had been indicated, and no gender differences in VCS have been reported. Results that showed a significant group-by-spatial-frequency interaction were further analyzed in step-down, two-tailed Student’s t-tests (α = 0.05), the equivalent of a univariate ANOVA, to determine which spatial frequencies accounted for the overall effect.

Results

Differences in mean VCS between the marine and land control groups were not statistically significant [F(1.85) = 1.70, p = 0.196], and the groups’ VCS profiles across spatial frequencies were normal and very similar [F(4,82) = 0.57, p = 0.685]. Therefore, the two control cohorts were combined (n = 87, average age = 45.4 ± 1.5 SEM, average education = 14.7 years ± 0.3 SEM) for comparison with the estuary cohort (n = 77, average age = 44.8 ± 1.9 SEM, average education 13.5 years ± 0.4 SEM). Group mean visual acuity scores and standard errors of the means of the left and right eyes combined were similar (p = 0.905) in the estuary (20:22.45 ± 0.70) and combined-control (20:22.25 ± 0.75) cohorts, suggesting that optical focus on the retina was similar in the two groups. However, group mean VCS, shown in Figure 1, with age adjustment was significantly lower across spatial frequencies in
the full estuary than the combined-control cohort (F(1,161) = 13.56, p < 0.001), with significant VCS group differences seen at 1.5 cycles/degree of visual arc in individual analyses at each spatial frequency. A significant group-by-spatial frequency interaction [F(4,158) = 4.79, p = 0.001] indicated that the VCS spatial frequency profiles of the groups were not parallel.

The normal peak in VCS at midspatial frequency (6 cycles/degree) seen in the control cohort was shifted to 3 cycles/degree in the estuary cohort due to the sharp drop at 6 cycles/degree. Significant age [F(1,161) = 9.69, p = 0.002] and spatial frequency-by-age interaction term [F(4,158) = 2.72, p = 0.032] reflected the normal decline of VCS with age in adults, but the two groups were not significantly different in age (Student’s t-test, p = 0.785). As shown in Figure 1, the VCS deficit in the full estuary cohort was entirely attributable to cohort members subsequently diagnosed as PEAS cases. VCS in estuary cohort noncases closely matched that of the combined-control cohort.

Questionnaire data were examined for each of the 77 members of the estuary cohort to determine if any members met the CDC case definition for PEAS. Although the estuary cohort members had not sought treatment at the clinic because of symptoms they attributed to estuary contact, 37 members were diagnosed with chronic PEAS. The prevalence of CDC-defined PEAS symptoms, and other symptoms reported by previous PEAS cases (19), reported by the cases were contrasted with those reported by all non-cases (40 from the estuary cohort and 87 from the combined-control cohort; Table 1). Symptoms reported by more than half of the cases were memory loss, headache, fatigue, eye irritation, sensitivity of the eyes to bright light, gastrointestinal distress (usually secretory diarrhea—diarrhea without intake), and shortness of breath. The other symptoms included in Table 1 were reported by less than half the cases, and a skin rash as observed in some acute PEAS cases (8) was seen in only 16% of cases. In contrast, few of the 18 symptoms listed in Table 1 were reported by the 127 noncases; the only symptom reported with prevalence as high as 5% in the noncases was cough.

Following CSM treatment for 2 weeks according to the standardized protocol, the prevalence of symptoms in the PEAS cases was dramatically reduced (Table 1). Only light sensitivity, memory loss, and muscle ache were still reported by more than 8% of the cases. Symptom prevalence in the non-cases was essentially unchanged following treatment with medications appropriate for their various diagnoses. CSM treatment was effective in restoring VCS to a normal level in patients with PEAS symptoms. Prior to treatment, all cases showed severe VCS deficits similar to those seen in previously reported PEAS cases (19). Group mean VCS in the cases prior to treatment, shown in Figure 2, were abnormally low at all spatial frequencies, but the largest deficit, about 60%, was seen at mid-spatial frequency. After CSM treatment, VCS showed significant recovery to control level [F(1,36) = 63.01, p = 0.001] overall and at each spatial frequency in individual analyses, and a normal spatial-frequency profile with peak sensitivity at mid-spatial frequency was restored [F(4,33) = 138.65, p < 0.001]. Visual acuity was unchanged in the cases following treatment (p = 0.661), indicating that the VCS enhancement was likely because of improvement in neurological function rather than optical refraction.

Three additional studies addressed potentially confounding issues for VCS testing and CSM treatment. First, VCS and visual acuity were measured in a healthy population free of estuary exposure and potentially confounding factors in order to investigate the effect of repeated testing at a 2-week interval. Visual acuity scores were unchanged (p = 0.453) between the first and second test sessions. A slight improvement in VCS over time was not significant [F(1,14) = 3.95, p = 0.067], and no change was observed in the VCS spatial frequency profile [F(4,11) = 0.65, p = 0.636] between the first and second test sessions (Figure 3). Second, the indicators of visual function were measured in an unexposed and confounder-free population taking CSM for hypercholesterolemia to again investigate VCS variability over time and to assess treatment effects on VCS in a population with no known neurotoxicant exposures. Neither visual acuity (p = 0.250), mean VCS [F(1,7) = 0.76, p = 0.412] nor the VCS spatial-frequency profile [F(4,4) = 0.14, p = 0.956] were altered after 2 weeks of CSM treatment (Figure 3). The data from both groups in both test sessions were comparable with the exception that mean VCS at the highest spatial frequency, 18 cycles/degree of visual arc, was slightly higher in the healthy (29.8) than the hypercholesterolemia (21.4) group, which likely reflects the difference between the mean visual acuity scores of the groups, 20:21.3 and 20:25.3, respectively.

Third, a double-blind, placebo-controlled, cross-over clinical trial compared the efficacy of CSM and placebo treatments on VCS and symptoms in PEAS patients. Although group-mean visual acuity (20:31.25) was not significantly affected by CSM treatment [F(1,7) = 1.10, p = 0.329], group mean VCS of all eight patients was significantly increased following CSM treatment [F(1,7) = 27.93, p = 0.001; Figure 4]. Furthermore, as indicated by the significant treatment by spatial frequency interaction [F(4,4) = 20.88, p = 0.006], the shape of the contrast sensitivity function was restored to normal; peak sensitivity was at midspatial frequency. The VCS deficit seen before treatment was greater at mid-to-higher than lower spatial frequencies. The 70% VCS reduction at midspatial frequency was restored following CSM treatment (p < 0.001). The group that received placebo before CSM treatment showed no improvement in VCS following placebo treatment but marked improvement following CSM treatment. The group that first received CSM treatment showed marked improvement, with no further improvement seen following placebo treatment.
The effects of treatment on reported symptoms are shown in Table 2. The eight patients reported 54 symptoms before CSM treatment but only 7 symptoms after treatment. The group taking placebo before CSM showed no improvement following placebo but marked improvement following CSM treatment. In the group assigned CSM therapy initially, the improvement in symptoms after CSM treatment was retained following placebo treatment. The symptoms reported most commonly at diagnosis were memory impairment, cough, headache, fatigue, skin rash, burning skin, eye irritation, secretory diarrhea, light sensitivity, and concentration difficulty. Less frequently encountered symptoms were shortness of breath, weakness, vertigo, abdominal pain, confusion, upper airway obstruction, and muscle cramp.

Discussion

In the current study we found that the ability to detect visual patterns, as indicated by measures of VCS, was significantly reduced in a cohort with residential and/or recreational exposure to TPC-inhabited estuaries relative to control participants of similar age and visual acuity. The statistical adjustment of VCS for age ensured that the group difference was not due to an age-distribution difference, and the comparability of visual acuity in the cohorts indicated that the VCS group difference was likely of neurological, rather than optical origin. The 37 PEAS cases identified among the 77 estuary cohort members accounted for the VCS deficit in the whole-estuary cohort; VCS in the estuary cohort noncases was comparable to that of the combined-control cohort. Prior to treatment, the group of PEAS cases reported many more symptoms listed in the CDC case definition for PEAS (12) and other symptoms reported by previous PEAS cases seen in the Pocomoke City clinic (19) than did the noncases. Following CSM treatment, the PEAS cases showed a statistically significant improvement in VCS coincident with symptom abatement. These results suggested that morbidity, predominate neurologically but including gastrointestinal, respiratory symptoms, and others, may be common among individuals living by or engaging in recreation in estuaries containing TPC. This correctable condition, defined by symptoms that are nonspecific when considered individually, becomes uniquely identifiable as a clinical syndrome, present in a reproducibly defined grouping, when associated with exposure without confounding factors, may have gone largely underdiagnosed and underreported. This situation may be rectified by proper symptom screening and use of VCS testing, followed by treatment with CSM.

All members of the estuary and control cohorts were eligible to enroll in the study because they had sought treatment at the clinic and met study inclusion criteria; population-based sampling techniques needed to estimate prevalence were not used in the study. The data reported here cannot be used to estimate prevalence of PEAS cases in the study area. The study associated morbidity and visual dysfunction with estuarine contact in the Pocomoke area in the absence of fish kills but where TPC-associated fish kills and coincident human illness were reported previously (8). However, no means were available to test the hypothesis that TPC toxin(s) exposure caused the VCS deficit or morbidity. Definitive attribution of PEAS to TPC must await identification of, and one or more tests for, the toxin(s) (6). It remains possible that unidentified estuarine exposures unrelated to TPC induced PEAS. Nonetheless, the comparability of the land and marine cohorts in VCS, the large number of study participants in the estuary and combined-control cohorts, and the large differences in VCS and symptom prevalence between the cases and non-cases indicate that the study results likely were not due to chance or sampling error. The control studies indicated that VCS measurements are stable over a 2-week interval and that CSM treatment does not affect VCS in a group with no suspected exposures to neurotoxins. These results suggest that the VCS deficit in the PEAS cases likely was related to contact with estuaries where TPC-induced toxicity is the only risk for neurotoxicity suspected to date.

The PEAS cases were treated with csm due to treatment results seen previously in anecdotal studies as well as the double-blind, placebo-controlled, cross-over, clinical trial confirming the efficacy of csm therapy in PEAS cases. CSM, a polyvalent too large for gastrointestinal absorption, was the first treatment approved for reducing cholesterol levels. The theoretical basis for CSM use in the PEAS cases was that toxin elimination rates can be enhanced through anion-exchange or other binding of CSM with toxins, thereby interrupting the enterotheric recirculation process through which toxins concentrated in bile are reabsorbed and systemically distributed, leading to toxin elimination. CSM has been used previously for detoxification in case studies or animal models of toxicity, including kepone (21,22), DDE (23), other organochlorine pesticides (24), polychlorinated biphenyl compounds (25), Clostridium difficile toxin (26,27), Escherichia coli and Vibrio cholerae toxins (28,29), one or more cytotoxins from at least one unidentified gastrointestinal microorganism (30,31), the mycotoxins ochratoxin A (32,33) and fumonisin B1 (34), the P fusium toxin zearalenone (35), the cyanobacterial toxin microcystin LR (36), and a toxin from the Chinese herbal product Jin Bu Huan (37). The plasma half-life of M1, the active metabolite of Arava

![Figure 4. Group mean spatial frequency profiles of visual contrast sensitivity from the double-blind, placebo-controlled cross-over clinical trial. Eight patients completed the clinical trial on the efficacy of cholestyramine treatment in PEAS cases. VCS before treatment was strongly depressed relative to after cholestyramine treatment in whole group. The group that took a placebo for 2 weeks prior to cholestyramine treatment showed no improvement after placebo. The group that took cholestyramine for 2 weeks prior to placebo retained the marked improvement in VCS after completing the placebo condition of the trial.](image-url)
impaired physical fitness, depression, irritability, bowel disease, allergy, sinus congestion, and other unconfirmed, unrelated medical conditions. Care should be taken by physicians not to overlook the possibility of PEAS involvement when assessing conditions involving multiple, concurrent, unexplained, cognitive, gastrointestinal, respiratory, and other symptoms, as well as syndromes in which unrelenting fatigue is a predominant symptom, in patients living in areas at risk for contact with TPC-inhabited estuaries.

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