

Neurologic Signs of Ciguatera Disease: Evidence of their Persistence

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Abstract. Ciguatoxins exert their effect on the voltage-sensitive sodium channels of the cellular membranes of all excitable tissues. This effect confers to ciguatera disease (CD) its neurologic hallmarks. A prospective study among French Polynesian adults over a two-month period was conducted to characterize and determine the persistence of neurologic symptoms of CD. We compared 47 patients with CD with 125 controls. In the acute phase of the disease, patients had mainly sensory disturbances as detected by an hypoesthesia on the palm of the hand and poorer sway performance compared with controls. Follow-up two months showed improvement of sway performance that eventually reaching control levels. However, for light-touch threshold, even if we observed a decrease threshold towards normal values, more than 50% of patients did not reach normal values 60 days after disease onset. Our results support the existence of neurologic impairments of CD and suggest their persistence for at least two months after onset.

INTRODUCTION

Besides the undeniable nutritional benefits on human health provided by marine products, seawater is also a natural reservoir for microorganisms that have the potential to cause illness in humans. Marine toxins are highly potent in living organisms, the time of symptom onset is very short, they are generally undetectable in seafood by human senses, and most toxins act on neural cells and particularly at the membrane level.^{1,2} Diseases induced by marine toxins are relatively well identified. Examples include amnesic shellfish poisoning, diarrhetic shellfish poisoning, neurologic shellfish poisoning, and ciguatera.^{1,2} Gastrointestinal and neurologic symptoms generally occur together in these types of intoxications, although they may vary in magnitude according to the toxins involved. However, these symptoms are generally transient (disappearing in a few days). This last feature sets ciguatera poisoning apart from other seafood intoxications in that several symptoms of ciguatera have been reported to exist for months.^{3–8} This unsolved particularity is still a stumbling block for the management of the disease.

Symptoms that appear long-lasting in ciguatera disease involve peripheral sensory and motor systems.³ Among these symptoms, paresthesia, dysesthesia, dizziness, ataxia, general weakness, and mood disorders are often reported. To this day, knowledge about chronic neurologic has been obtained mostly from isolated case reports.^{8,9} Studies with detailed neurologic examinations are scarce and for the most part address patients who required hospitalization.^{4,6,8,10–13} However, both clinical case reports and epidemiologic studies indicated peripheral and central neurologic involvement in impairment in ciguatera disease, which corroborate findings from experimental studies.^{14–17}

In case reports, a recurrence of symptoms has often been observed. This reoccurrence seems to be triggered by a number of factors including fish consumption, alcohol use, and physical activity.^{18–22} Moreover, it is well recognized that fish consumption by humans is the principal source of polyunsaturated fatty acids (PUFAs) and methylmercury, which have

neuroprotective and neurotoxic actions, respectively.^{23–25} Therefore, while examining the link between ciguatera and its neurologic effects, it is essential to consider these additional and potentially confounding factors.

We conducted a prospective study in French Polynesia to characterize neurologic symptoms of ciguatera disease with a special focus on peripheral sensory and motor systems, and to determine their persistence over time.

SUBJECTS AND METHODS

Study design. This prospective study compared a group of 65 adult patients with ciguatera disease with a group of 130 healthy people. It was conducted in French Polynesia between March 2001 and June 1, 2004. The study included blood sampling and a detailed neurologic evaluation using a standardized para-clinical and clinical neurologic examination that included motor and sensory tests conducted at three points in time (T0 = 0–7 days after seafood ingestion, T2 = 2 weeks after disease onset, T3 = 8 weeks after disease onset). Patients were asked to participate in all three sessions, healthy subjects participated only in one session and, both participant groups signed an informed consent form. This study was reviewed and approved by the Laval University ethical committee, the ethical committee of the Pan American Health Organization, and the ethical committee of French Polynesia.

A ciguatera case was defined as the acute onset of neurologic symptoms after (< 12 hours) consuming a good-tasting local reef fish; typically these acute symptoms included paresthesia and troubles with cold perception with or without gastrointestinal symptoms such as vomiting and diarrhea. Exclusion criteria were any of the following: 1) < 18 years of age, 2) pregnancy, 3) leprosy or neurologic disease, and 4) a ciguatera diagnosis more than 7 days after the onset of the disease. Unexposed participants were volunteers from the Tahiti and Moorea Islands who responded spontaneously to a press release about the study (90% of controls and 10% were friends of patients). Because no simple measures of ciguatoxins were available, we ensured that controls were ciguatera-free by asking them if they had consumed reef fish in the last 12 hours before recruitment and if they were experiencing any gastrointestinal or neurologic symptoms typically associated with ciguatera disease. Additionally, people who had had

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ciguatera disease during the year before the study period were excluded from the unexposed group. According to these criteria, no healthy participant was excluded. However, we excluded 18 patients and 5 healthy subjects because of missing data on neurologic testing.

Neurologic evaluation. The neurologic clinical examination was a standardized 20-minute test. Two physicians from our research team performed this evaluation. To reduce multiple evaluator bias, physicians completed a standardized checklist of symptoms. All participants also answered questions on symptoms experienced at the time of the interview.

Motor evaluation. Neuromotor evaluations were performed by a nurse and a PhD student. Specific motor functions were quantified with a computerized test (Computerized Adaptive Testing System [CATSYS]; Danish Product Development Company Ltd., Snekkersten, Denmark). Reliability criteria of the tests such as validity, specificity, and

sensitivity have been verified in a number of populations.^{26,27} Motor evaluations were performed according to the same specific sequence, i.e., reaction time (right and left hand), sway measurements (open and closed eyes), tremor evaluation (right and left hand), pronation/supination test (right and left hand), and finger tapping (right and left hand). This sequence was developed to minimize the influence of stress on tremor evaluation. The testing period of each test and metronome beat was the same as that used by Després and others.²⁸ Specific parameters provided by CATSYS test system are shown in Table 1.

Light touch threshold exploration. This evaluation of tactile perception thresholds was done by light- and deep-touch tests known as Semmes-Weinstein filaments. During this test, nylon filaments of various diameters (1.65–6.65 mg) were successively applied to the skin on the palm of the hands and the feet of the subject²⁹ (Figure 1). According to the manufac-

TABLE 1
Definition of characteristics of the computerized adaptive testing system selected for the analysis*

Parameters	Definition	Scale*
Reaction time (RT)	Mean of all reaction times obtained during the test. Unit: Second	Larger values indicate poorer performance
Finger tapping		
Rhythmic regularity (sP)	Rhythmic regulation to keep up precision. Unit: dimensionless	Values always positive, smallest values indicate better regularity
Precision (P)	Mean of accuracy of contact in relation to metronome sound. Unit: second	Value nearest zero indicates a better precision. Larger values indicate better performance
Maximum frequency	Maximum frequency obtained in Hz	
Pronation and Supination		
Rhythmic regularity (sP)	Rhythmic regulation to keep up precision. Unit: dimensionless	Values always positive, smallest values indicate better regularity
Precision (P)	Mean of accuracy of contact in relation to metronome sound. Unit: second	Value nearest zero indicates a best precision. Larger values indicate better performance
Maximum frequency	Maximum frequency obtained in Hz	
Tremor		
Tremor intensity (TI)	The root mean square of acceleration recorded in the 0.9–15 Hz band. Unit: $m*s^{-2}$	Larger values indicate more tremor
Center frequency (F50)	The median frequency of the acceleration in the 0.9–15 Hz band. Unit: Hz or s^{-1}	
Frequency dispersion (SF50)	Degree of irregularity of the tremor. Frequency band centered around the median frequency that contains 68% of the power. Unit: Hz	A regular tremor has a small SF50 indicating that most of the area is within a narrow frequency band (e.g., pathologic tremor)
Harmonic index (HI)	Compares the tremor frequency pattern of a single harmonic oscillation, which has an HI = 1.00. Unit: dimensionless	HI decrease when the tremor is composed of many oscillations
Tremor index (T index)	Overall summary index, which is the root mean square of Z scores of the four previous measures. Unit: dimensionless	Above 1.55 tremor may be considered as abnormal ³⁹
Postural sway		
Mean sway	Mean distance from the mean force center position to all recorded force center positions during the test. Unit: mm	Larger values indicate poorer ability in postural sway
Transversal sway	Mean of the recorded x-direction values of the force center in a coordinate system. Unit: mm	Larger values indicate poorer ability on transversal sway
Sagittal sway	Mean of the recorded y-direction values of the force center in a coordinate system. Unit: mm	Larger values indicate poorer ability on sagittal sway
Sway area	Area of the smallest polygon including the total trajectory of the force center in the horizontal plate plane. Unit: mm^2	Larger values indicate poorer ability in postural sway
Sway velocity	Average travel speed of the force center in the horizontal sway plate plane calculated by dividing the total length of the force center trajectory in mm by the recording period length (in second). Unit: mm/sec	Larger values indicate poorer ability in postural sway. This measure was proposed as the most sensitive parameter ³²
Sway intensity	Higher value recorded in any direction of the force center in a coordinate system. Unit: mm	Larger values indicate poorer ability in postural sway

* Adapted from Després and others.²⁸

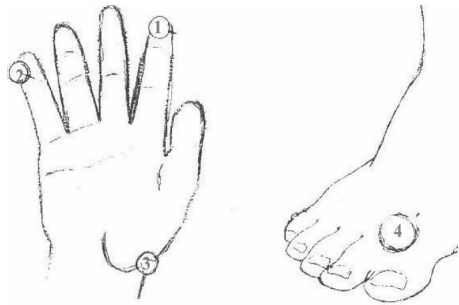


FIGURE 1. Hand and foot sites in Semmes-Weinstein monofilaments examination.

Legend

- 1 Median nerve
- 2 Ulnar nerve
- 3 Radial nerve
- 4 La5 area

turer, in normal populations the threshold is 0.07 grams. A perception value under this threshold is qualified in our study as hyperesthesia. Above this value the results are qualified as hypoesthesia and no sensation is qualified as anesthesia.

Blood sample. We measured γ -glutamyltransferase as indicator of alcohol consumption, total mercury, and PUFA concentrations in blood of all participants. Fatty acids were analyzed by gas-liquid chromatography and total mercury was evaluated by cold vapor atomic absorption spectrometry.

Data analysis. Summary data is expressed as means and standard deviations for continuous variables or proportions for categorical variables. Values were compared by *t*-test, Fisher's exact test, or chi-square test as appropriate.

At T1, analysis of variance was used to examine the potential association between dependent continuous neurologic variables (motor function or light-touch threshold) and factors recorded in the study. Multivariate analysis (covariance analysis) was performed to examine the relationship between neurologic functions (continuous outcomes) and ciguatera exposure, after adjusting for potential confounders. Variables were considered as confounders when their inclusion in the model modified the regression coefficient of exposure by more than 10%. For dichotomous outcomes, logistic regression was used and potential confounding was also evaluated.

To evaluate the persistence of signs (continuous outcomes) (i.e., T2 and T3), we treated data as repeated-measure outcomes using the mixed model approach.³⁰ For dichotomous outcomes, logistic regression with the generalized estimating equation method adjusting for within-subject correlation arising from repeated measures were used to compare changes in proportion from baseline to two months in cases.

All statistical analyses were performed with a significance threshold of $\alpha = 5\%$. Statistical treatments were performed using SAS software release 8.02 (SAS Institute Inc., Cary, NC).

RESULTS

Acute symptoms and signs of ciguatera disease. Table 2 shows anthropometric, demographic and lifestyle characteristics and blood concentration of the two groups retained in the analysis. Patients and healthy people were similar except in sex proportion. Subsequent analysis was then performed considering this unbalanced representation.

The two groups differed significantly in some neurologic test results (Figure 2), and ciguatera patients always showed a higher proportion of positive signs compared with healthy

TABLE 2

Description of demographic lifestyle characteristics of exposed and unexposed participants at the time of onset (T0)*

	Exposed (n = 47)	Unexposed (n = 125)	P
Sex (%)			0.025†
Female	55.3	36	
Male	44.7	64	
Ethnic origin (%)			0.139‡
Polynesian	80.3	64.0	
European	6.4	04.8	
Chinese	04.3	12.8	
Mixed	08.5	18.4	
Age (years), mean (SD)	46.3 (10.3)	46.3 (8.9)	0.994§
BMI (kg/m ²), mean (SD)	28.0 (5.6)	27.6 (5.0)	0.682§
Tobacco (%)			0.473†
Smokers	40.4	33.3	
Nonsmokers	59.6	66.7	
Alcohol (%)			0.360†
Consumers	63.8	71.1	
Nonconsumers	36.2	28.9	
Regular practice of sports (%)			0.175†
More than once a week	44.7	56.5	
Once a week or less	55.3	43.5	
Past event of ciguatera (%)			1.000†
At least one	57.5	58.5	
None	42.5	41.5	
γ -Gt, mean (SD)	43.6 (53.3)	40.5 (39.1)	0.289§
Hg-T (nmol/L), mean (SD)	118.0 (68.0)	101.2 (62.7)	0.132§
EPA + DHA, mean (SD)	3.3 (1.58)	3.99 (2.63)	0.095§

* BMI = body mass index; γ -Gt = γ -glutamyl transferase; Hg-T = total mercury; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.
 † By two-sided Fisher's exact test.
 ‡ By Pearson's chi-square test.
 § By analysis of variance.

participants. In the exposed group, we observed positive signs in Romberg testing with open and closed eyes, errors in hot/cold perception, and superficial pain and impairment of the bone tendon reflex in each upper and lower limb ($P < 0.0001$). No patient had cranial nerve paresis. Few ciguatera patients

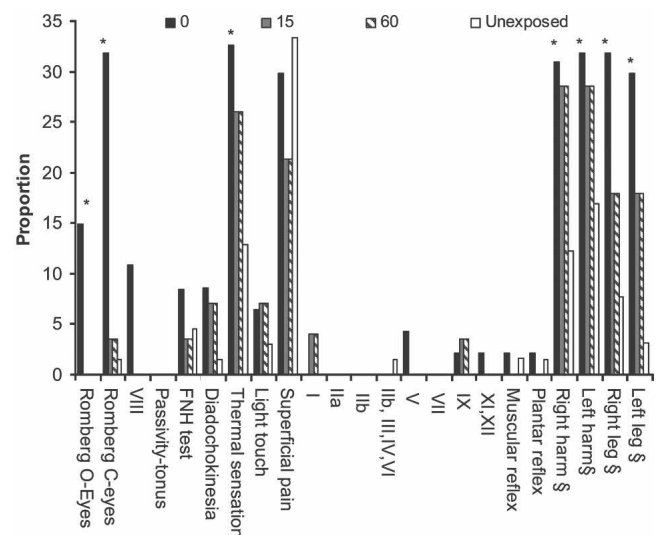


FIGURE 2. Comparison of neurologic examinations between unexposed and exposed participants. * $P < 0.05$; I–XII = cranial nerves; § = bone, tendon reflex. White bars = unexposed; dark bars = exposed at disease onset; gray bars = 15 days after disease onset; dashed bars = 2 months after disease onset. FNH = focal nodular hyperplasia. Proportion is in percent.

had impairments in coordination ability and the difference compared with unexposed participants was not significant. Moreover, at the onset, most prevalent symptoms were paresthesia (distal and proximal part) (93%), dysesthesia (discomfort on the tongue and throat) (91%), and myalgia and arthralgia (80%).

At the time of onset, patients demonstrated a higher light-touch threshold on hands than controls. This was statistically significant for most of the nerves in both hands tested (Figure 3). Similar differences between exposed and unexposed were observed in the left foot but not in the right foot. These results were obtained after adjustments for sex, age, blood mercury levels, and fatty acid concentrations of the participants.

Manual coordination performances were similar between groups except for isolated tests (2 parameters among 20 evaluated) such as precision of finger tapping ($P = 0.02$) and frequency dispersion in the right hand ($P = 0.02$). In these tests, patients showed poorer performances.

On sway evaluation, we observed significant differences between groups essentially in closed-eye condition. As shown in Figure 4, without visual input, patients had poorer postural sway performance than healthy participants. These results were obtained after controlling for co-variables significantly related to postural sway such as age, sex, regular physical activity, blood mercury levels, and eicosapentaenoic acid and docosahexaenoic acid concentrations in blood. In the open-eye condition, intensity of sway was the only parameter for which a statistical difference was observed between the two groups. Patients showed a higher value of intensity than healthy participants.

Follow-up of symptoms and signs of ciguatera disease. At the time of recruitment, all patients agreed to participate in all interviews. However, among patients included in the study, only 72% of patients completed the second session and 60% of patients met the research team for the third session. According to the severity scale of the disease obtained at the

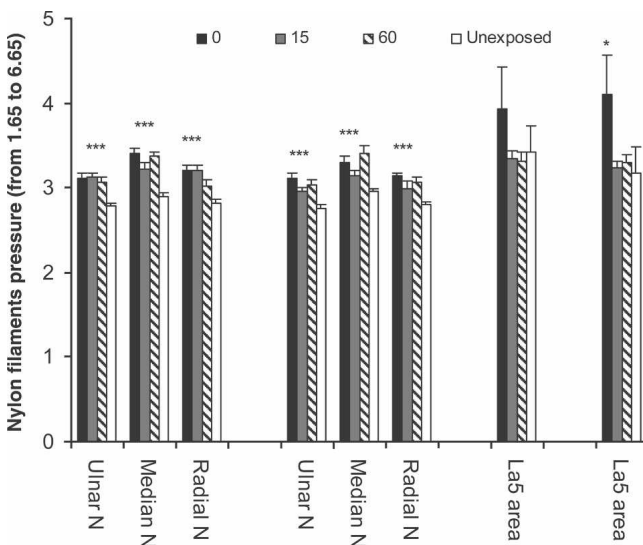


FIGURE 3. Comparison of light-touch threshold between unexposed and exposed participants. * $P < 0.05$; white bars = unexposed; dark bars = exposed at disease onset; gray bars = 15 days after disease onset; dashed bars = 2 months after disease onset. Error bars show standard deviation.

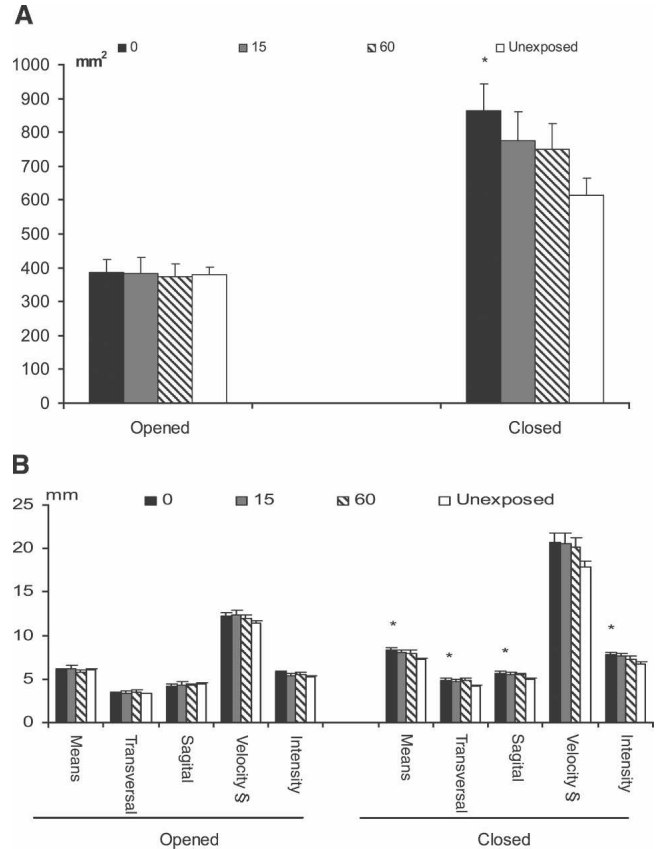


FIGURE 4. Comparison of sway performances between unexposed and exposed participants. **a**, sway area in mm^2 ; **b**, other parameters tested by sway plate. § = mm/sec ; * $P < 0.05$. All means and P values were adjusted for sex, age, and regular physical activity. White bars = unexposed; dark bars = exposed at disease onset; gray bars = 15 days after disease onset; dashed bars = 2 months after disease onset. Error bars show standard deviation.

time of onset, patients who completed all sessions were similar to others ($P = 0.71$). These groups were also similar in age ($P = 0.68$), sex ($P = 0.14$), body mass index ($P = 0.41$), smoking ($P = 0.76$), regular physical activity ($P = 0.56$) and past occurrence of ciguatera ($P = 1.00$). The only difference observed was for alcohol consumption ($P = 0.02$). The proportion of patients who reported consuming alcohol was smaller in patients who completed all sessions.

For several neurologic tests for which we had observed an impairment at time of onset, we also observed a recovery of the neurologic function two months later (Figure 2). However, we observed no change in hot/cold perception ($P = 0.25$).

Adjusting for three time periods, sex, and age, we observed that some parameters of the light-touch threshold evaluation remained significantly higher among cases at 60 days after the onset of the disease compared with controls (Figure 3). In feet light-touch, exposed patients at the end of the follow-up did not show higher light-touch thresholds than unexposed participants. For the time reaction test on both hands, there were no significant differences between patients tested at the end of the study and the unexposed group.

On postural sway in open-eye and closed-eye conditions, all parameters measured at second and third testing sessions were not significantly different from controls (Figure 4).

These results were obtained after adjustment for three time periods of testing, sex, and age.

DISCUSSION

The stated goal of this prospective study was to characterize neurologic abnormalities of ciguatera disease using a standard neurologic examination and light-touch threshold evaluation and motor function examinations. Clinical findings included static and dynamic ataxia, general impairment of the bone tendon reflex (markedly depressed or abolished) in the upper and lower limbs, diminishing sensation to light touch, and errors in hot/cold perception. The light-touch threshold evaluation showed a significant impairment of tactile perception on the palms of hands compared with controls, but this finding was not clearly present on the feet. In addition to clinical signs such as paresthesia and cold allodynia, loss of tactile sensation in glove-type distribution, and alteration of gait and postural sway may indicate impairment of the lemniscal sensitivity observed in sensory neuropathy.

Our results are in accordance with recent studies that suggest that polyneuropathy of ciguatera poisoning is a mixed sensory neuropathy.³¹ Interestingly, we did not observe the classic glove and socks distribution typically encountered in this type of polyneuropathy. In light of our results, we suspected that the asymmetry observed is related to the anthropologic fact that most of French Polynesians walk regularly without shoes or wear typical thong sandals that hurt the La5area evaluated in this study. Nevertheless, peripheral neuropathy has previously been observed³² in numerous isolated case reports in which patients had severe poisoning.^{4,8,9,13} The specific action of ciguatoxins on voltage-dependant sodium and calcium channels,^{2,14,17,20,33,34} which induce slowing of sensory and motor nerve conduction velocities and a diminishing amplitude of sensitive and motor-evoked potential, enabled us to link ciguatera disease with the axonal channelopathies reported by Gutmann.³⁵

Electrophysiologic evaluations on humans severely intoxicated and animals suggested a sensitivity of myelinated and unmyelinated fibers to the deleterious actions of cardiotoxin (CTX).¹³ In addition, Australian researchers have linked altered cold perception to intense nerve depolarization in peripheral small-A and C-polymodal nociceptor.³⁶ These fibers are known to transfer tactile, thermal sensitive information, and are also involved in itching sensation. Impairment of sensitivity observed in our patients was reinforced by a large proportion of our patients who reported itching, leading us to suggest dysfunction of small fiber as observed recently in the Cook Islands.³¹ However, inconsistency among human neurophysiologic evaluations and differences in clinical observations suggest the existence of a gradient in polyneuropathy induced by ciguatera disease probably in relation to the quantity of circulating CTX and/or the involvement of other toxins.^{4,9} This could explain differences observed between our patients.

After the onset of disease, results of neurologic examinations were normal, and no differences were observed between patients and the control group, even if 30% of the patients still had subjective complaints such as overall weakness two months after disease onset. Moreover, sway performances of patients reached values of the control group. Therefore, we

may conclude that normal sway was restored. Interestingly, we observed no significant differences in hand coordination between the two groups. Overall, among the functions evaluated in the follow-up, only light-touch threshold was still impaired two months after disease onset. Compared with people without ciguatera, some threshold values measured in patients were still high, essentially at the palm of the hands level. These results concur with progressive regression of neurologic signs previously observed.^{3,4,9}

We observed no effect of ciguatera disease on hand coordination. However it is possible that our measure of rapid alternating movement may not be sufficiently precise to characterize subtle alterations in diadochokinesia as proposed by Desprès and others.²⁸ Thus, to verify if manual ability is undeniably impaired, other tests such as diadochokinesimeter should be used.³⁷ Desprès and others discussed intra-individual variability in testing that was also used in our study.²⁸ This variability may have weakened associations observed in this study. A similar conclusion may be applied to our results on the evaluation of tactile threshold. At the neurologic examination, variability was also observed even if standardized neurologic evaluation was used by our two neurologists. In this case, as proposed by Shinar and others,³⁸ neurologist variability may have reduced the strength of the relationship observed. Possible errors in neurologic assessment could have led to an underestimation of the magnitude of the true exposure relationship.

Despite the above limitations, our study showed several new aspects of ciguatera disease. Among our patients who may be described as mildly intoxicated, we observed clinical signs consistent with mild sensory neuropathy that predominantly affects the lemniscal system. These signs, which apparently resolved progressively, had not totally disappeared two months after the onset of the disease.

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