Neurologic Outcomes of Toxic Oil Syndrome Patients 18 Years after the Epidemic

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Toxic oil syndrome (TOS) resulted from consumption of rapeseed oil denatured with 2% aniline and affected more than 20,000 persons. Eighteen years after the epidemic, many patients continue to report neurologic symptoms that are difficult to evaluate using conventional techniques. We conducted an epidemiologic study to determine whether an exposure to toxic oil 18 years ago was associated with current adverse neurobehavioral effects. We studied a case group of 80 adults exposed to toxic oil 18 years ago and a referent group of 79 adult age- and sex-frequency–matched unexposed subjects. We interviewed subjects for demographics, health status, exposures to neurotoxicants, and responses to the Kaufman Brief Intelligence Test (K-BIT), Programa Integrado de Exploracion Neuropsicologica (PIEN), and Goldberg depression questionnaires and administered quantitative neurobehavioral and neurophysiologic tests by computer or trained nurses. The groups did not differ with respect to educational background or other critical variables. We examined associations between case and referent groups and the neurobehavioral and neurophysiologic outcomes of interest. Decreased distal strength of the dominant and nondominant hands and increased vibrotactile thresholds of the fingers and toes were significantly associated with exposure to toxic oil. Finger tapping, simple reaction time latency, sequence B latency, symbol digit latency, and auditory digit span were also significantly associated with exposure. Case subjects also had statistically significantly more neuropsychologic symptoms compared with referents. Using quantitative neurologic tests, we found significant adverse central and peripheral neurologic effects in a group of TOS patients 18 years after exposure to toxic oil when compared with a nonexposed referent group. These effects were not documented by standard clinical examination and were found more frequently in women. *Key words:* **case–referent study, environmental food epidemic, exam, long-term effects, neurobehavioral tests, toxic oil syndrome.** *Environ Health Perspect* **111:1326–1334 (2003). doi:10.1289/ehp.6098 available via** *http://dx.doi.org/* **[Online 9 April 2003]**

Toxic oil syndrome (TOS) appeared as a new disease in Spain in 1981. TOS continues to be of great interest to epidemiologists and toxicologists because it is an example of the potential risks of adulterated food, as well as showing the importance of chemical environmental exposures in the development of autoimmune diseases (Gelpi et al. 2002). Although TOS patients have a mortality rate similar to that of the Spanish population as a whole, many survivors have been left with a variety of handicapping conditions (Gomez et al. 1998). The numerous social, clinical, and research problems dealt with during this epidemic have provided a basis for the study of other similar episodes, such as the eosinophilia-myalgia syndrome (EMS) epidemic (Kilbourne 1992), and other recent important problems in food processing and sales, such as new-variant Creutzfeld-Jacob disease (Tyler 2003) and the recent episode of contaminated chicken in Belgium (Van Larebeke et al. 2001).

The first case of the TOS epidemic was reported on 1 May 1981 in Torrejón de Ardoz, Province of Madrid (Tabuenca 1981). TOS resulted from the consumption of rapeseed oil that had been denatured with 2% aniline under the pretext that it was for industrial use; the oil had been refined in an attempt to remove the aniline and then illicitly sold as pure olive oil for human consumption (Tabuenca 1981). High temperatures and extreme vacuum conditions during the refining process led to a reaction of the aniline with fatty acids and tryglicerides, which are basic in regular oils, producing two different new families of compounds: fatty acid anilides and esters of the phenyl amino propanediol. More than 100 different compounds from these two families have been described in these oils, and their toxicologic mechanisms are still not well known (Gelpi et al. 2002; Posada de la Paz et al. 2001).

During the first month of the epidemic, about 10,000 persons became ill, and by the time the official patient registry closed, it contained the names of more than 20,000 persons who were affected by TOS. TOS developed in three clinically distinct phases now referred to as acute, intermediate, and chronic (Abaitua Borda and Posada de la Paz 1991; Posada de la Paz et al. 2001). The acute phase was characterized by noncardiogenic pulmonary edema with dyspnea, headaches, asthenia, itchy scalp, rash, abdominal pain, fever, and eosinophilia. Severe myalgias and muscle cramps marked the end of the acute phase.

After the first 2 months of illness, patients typically entered an intermediate phase, lasting about 2 months. This phase was characterized by frequent changes in signs and symptoms. Clinical features frequently observed included sensory neuropathy in 55% of patients and intense myalgia in 47.4%. Other findings were dysphagia, pulmonary hypertension, thromboembolic phenomena of the large vessels in 1.8% of the patients, marked weight loss, hepatic cholestasis, and induration of the skin followed by skin infiltration. High levels of peripheral blood eosinophils, hyperglycemia, and elevated triglycerides and cholesterol were also observed.

Around 59% of TOS patients progressed to a chronic phase with features of scleroderma, motor and sensory polyneuropathy, carpal tunnel syndrome, joint contractures, myalgias, and muscle cramps. Cognitive symptoms, such as memory loss and depression, have also been reported during the chronic phase of TOS (Abaitua Borda and Posada de la Paz 1991).

Since the end of the 1980s, most patients have experienced remission of the main clinical features, but some patients still show substantial neurologic sequelae such as myalgias, cramps, and contractures, and many continue to complain of other symptoms that may be of neurologic origin (Abaitua Borda and Posada de la Paz 1991). Often these patients' complaints have been vague or difficult to assess, and some have been mistakenly interpreted as

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A. Huidobro served as a consultant for selection of the written psychologic tests.

This work was supported by grants EU/99/00229, EU/99/002216, EU/99/038803, and EU/99/038816 from the World Health Organization Regional Office for Europe.

The authors declare they have no conflict of interest.

Received 8 November 2002; accepted 8 April 2003.

fictitious or exaggerated. As a result, some TOS patients may have been incorrectly classified as "chronic complainers," when instead they suffer from a genuine neurologic disorder.

A study that used the Nottingham Self-perceived Health Profile to evaluate a subcohort of TOS patients found that, as a group, TOS patients felt that they were in very poor health and that they suffered from a number of health problems (Gomez et al. 1998).

Although neurologic findings may be difficult to quantify, within the last few years techniques have been developed to measure neurologic abnormalities more accurately (Gerr et al. 1990, 1991; Letz 1991). Quantitative neurologic testing has been successfully used to characterize other diseases with subtle neurologic findings, such as the epidemic of optic and peripheral neuropathy that occurred in Cuba (Cuba Neuropathy Field Investigation Team 1995); EMS, a disease clinically similar to TOS (Philen and Posada 1993; Sullivan et al. 1996); and other diseases related to toxic environmental exposures (Stokes et al. 1998).

The hypothesis of this study was that TOS patients who have central or peripheral neurologic symptoms, which may be difficult to relate to specific neurologic findings on clinical examination, have neurologic abnormalities that can be identified and measured objectively using quantitative neurologic testing and can be compared with a referent group from the same geographic area. We compared the results of analogous items on the clinical neurologic examination with those of the quantitative neurologic examination in TOS patients. These data were used to determine which quantitative examinations yielded more information than the clinical neurologic examination, as well as to guide future decisions on the use of the quantitative neurologic examination in the TOS cohort.

Materials and Methods

We used a case–referent study design to assess the possible neurologic pathology in TOS patients.

Subjects

Setting. All TOS case participants and healthy referent participants were chosen from the Alcorcón locality in the southern part of the Madrid province, one of the areas affected by TOS in 1981, with 1,400 registered patients. All interviewing, testing, and other parts of the study were performed in the Hospital Fundación Alcorcón, Alcorcón (Madrid Province, Spain).

Sampling. We used a simple random sample of the TOS patients who were registered in Alcorcón at the time the official TOS census was done. Each TOS patient who was known to be living in the Alcorcón area was assigned a random number, and those random numbers were then sorted in ascending order. Patients were then contacted in numerical order until our sample size of 80 TOS patients was reached. The referent group was recruited from friends or family members living in the same geographic area. The case (exposed) group consisted of 80 adults who had been exposed to toxic oil 18 years ago, who had developed a clinical case of TOS, and who were then frequency-matched for age (± 5 years) and sex to a referent (unexposed) group of 79 adults. Participants selected as the reference population were required to report being free of signs of illness, although they could have had the same probability of being exposed as the cases.

Case definition. All TOS case patient participants were required *a*) to be registered in the 1985 TOS patient registry and in the REVCEN (acronym of the Spanish "revision of the census," the official TOS morbidity registry containing clinical information from 1981 to 1988) (Kilbourne et al. 1992); *b*) to have lived in Madrid Province, Alcorcón locality, in 1981 at the time of developing TOS; and *c*) to reside in Madrid Province, Alcorcón locality, during 1998–1999 (the time period when participants were enrolled and clinical and quantitative neurologic examinations were performed). In addition, participants had to be ≤ 65 years of age at the time the study was conducted.

Exclusions. TOS patients were selected among those living in Alcorcón during the epidemic onset, but one of the conditions for entering the study was to live in Alcorcón at the beginning of the study. Participants with diagnoses other than TOS that can result in neuropathy, including diabetes; renal disease; cerebrovascular accidents; alcoholism; or head, spinal cord, or other neurologic trauma, were excluded from the study. Pregnant women, persons unable to consent, and those unable to physically collaborate with the testing requirements were excluded (Table 1). On the other hand, selection of the referent group was made starting from cases. It was imperative that this group had previously fulfilled the same exclusion criteria as the cases. Additionally, a few participants were excluded from a particular test because of problems specific to that examination (i.e., participants with trauma or other injury to the hand or arm who were unable to complete motor strength measurements).

Recruitment. A meeting was held with the local TOS patient association in Alcorcón, informing the members of the objectives of the study and seeking their participation. Subsequently, all potential study participants were contacted via the local TOS patient association, first via a letter requesting their participation, followed by a phone call to schedule an interview. TOS patients thus contacted were interviewed in person and requested to participate, and signed a consent form at the time of the interview.

Data Collection

Questionnaires. A questionnaire was administered by a trained interviewer to each participant. Neurologic signs and symptoms, history of neurologic disorders, occupational and environmental exposure histories, residential history, medication use, dietary factors, smoking, alcohol use, and other exposure information were assessed for all participants and, if appropriate, adjusted for in the analysis. Information on demographics, past and current health, past exposures to neurotoxicants, and responses to the Goldberg Depression Inventory (Spanish translation) (Montón et al. 1993) were also collected by personal interview.

Neurologic examination. All participants were examined by one of two neurologists from Hospital Fundación Alcorcón, both of whom have extensive experience in TOS patient care, with special attention given to signs and symptoms of TOS and its related neurologic findings. Results were recorded in a standardized form.

Neurobehavioral tests. Medical testing consisted of a battery of neurobehavioral tests used to determine the functional status of the central nervous system (CNS), the peripheral nervous system (PNS), and the autonomic nervous system (ANS). These tests were administered by computer with the help of specially trained nurses. Detailed descriptions of how to perform these tests have been published elsewhere (Baker et al. 1985; Gerr et al. 1990, 1991; Letz 1991).

Vibrotactile threshold testing. Cutaneous vibrotactile thresholds were obtained for both index fingers and great toes using a portable vibrometer (Vibratron II; Physitemp, Inc., Clifton, NJ, USA) producing sinusoidal oscillation at 100 Hz. The results are reported in $\log_{10}$ micrometers of vibration amplitude. The "method of limits" protocol used has

Table 1. Reasons for nonparticipation of TOS patients in the study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

Cause/refusal	No.[a]
Did not fulfill inclusion criteria	
No longer live in Alcorcón	6
Death	2
Diagnosed with diabetes	2
Pregnancy	1
Down syndrome	1
Unable to locate	1
Refusals	
Absolute refusal	46
Work related	13
Non-TOS medical reason	4
Family responsibilities	3
Denied TOS	1

[a]TOS patients contacted, 160; nonparticipants, 80; total TOS participants, 80.

been shown to be reliable and time efficient (Gerr et al. 1990; Gerr and Letz 1988, 1993). Higher values indicate poorer sensory function. The vibrotactile threshold is a very useful measure for assessment of large, myelinated nerve fiber function, the fiber type most commonly affected by toxic exposures, including TOS. For a toxic axonal neuropathy, the lower extremities are likely to be more substantially affected than the upper extremities, although in this study some toxic effects were measured in both the upper and lower extremities.

Hand strength dynamometry. Bilateral hand strength dynamometry was performed on all study participants to assess neuromuscular function. Grip strength and pinch strength were measured by means of an adjustable-handle Jamar dynamometer and a B&L pinch gauge (Asimow Engineering Company, Santa Monica, CA, USA), using the method and instructions of Mathiowetz et al. (1984).

Standing steadiness testing. Standing stability was measured using a standard, commercially available force platform (AccuSway Platform; Advanced Mechanical Technologies, Inc., Waltham, MA, USA). Timing and data recording were accomplished by a dedicated IBM-PC–compatible laptop computer. The method used for measurement of standing stability has been described previously (Letz and Gerr 1995). Subjects, in stocking feet, were asked to stand as still as possible on the platform with hands at their sides either while fixating visually on a 2-cm-diameter circular mark on the wall, or with eyelids closed. Three trials with eyes open and three trials with eyes closed, 25 sec each, were alternated. The primary outcome variable analyzed was mean sway speed in centimeters per second (equivalent to the total length of the sway path divided by 25) averaged over the three eyes-closed trials.

Heart rate variability. Heart rate variability was obtained by measuring the interval, in milliseconds, between successive R-waves of the electrocardiogram. Surface electrodes were placed on the wrists and leg of the study participant. A differential amplifier (DAM-50; World Precision Instruments, Sarasota, FL, USA) and an IBM-compatible personal computer equipped with an analog-to-digital converter (Microstar Laboratories, Portland, OR, USA) were used for processing of the electrocardiogram signal. We created custom software to capture and store the interval between successive R-waves of the digitized signal. The primary outcome of this measure is the coefficient of variation during rest and the coefficient of variation during a period of deep breathing. Other variables explored included change in heart rate between resting and deep breathing and change in the coefficient of variation between resting and deep breathing (Murata and Araki 1991).

CNS testing. Tests of CNS function were a combination of a few manually administered neuropsychologic tests and a selection of computer-administered tests from NES2 (Baker et al. 1985) and NES3 (Baker et al. 1988; Letz et al. 1996). Motor tests were emphasized, with a sampling of other important CNS functions. The tests administered are described briefly below. Total administration time for all of these CNS tests was approximately 60 min. The NES2 tests (Version 4.75) were administered on a Toshiba 3200Sx computer (Toshiba America Electronic Components, Irvine, CA, USA) with an NES2 joystick, and the NES3 tests (Version 1.02) (Baker et al. 1985; Letz 1991) were administered on a Fujitsu Point 510 pen-based computer (Toshiba America Electronic Components) with external audio speakers.

In the grooved pegboard test, the subject must place 25 notched pegs into a board with 25 matching holes. The time taken to insert all 25 pegs is recorded for dominant and nondominant hands. The finger-tapping test measures motor quickness and coordination. The participant presses a button as many times as possible within 30-sec trials. After a practice trial, one trial each is performed with the preferred hand, the nonpreferred hand, and both hands alternating. The hand–eye coordination test evaluates manual dexterity and coordination. The participant uses a joystick to trace a large sine wave pattern on the video display. Vertical deviation from the wave pattern is recorded (as root mean squared error). Five trials are given; the mean of the two best trials is used as the summary measure. The simple reaction time test measures motor speed and sustained attention. The subject presses a joystick button as quickly as possible after a large square appears in the middle of the computer screen. Fifty trials are administered, and the preferred summary measure is the mean reaction time of the last 40 trials.

Several tests measured cognitive functions. The digit symbol test is a modification of the Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale–Revised (Letz et al. 1996). It measures coding skills, attention, and concentration. Symbols are matched with the digits 1 through 9 in a "key" at the top of the screen, and the participant must indicate which of the symbols in scrambled order at the bottom of the screen is matched with a test stimulus presented in the middle of the screen. The response latencies for completing three sets of nine pairs are recorded, and the preferred summary measure is the total time to complete the 27 stimuli.

The sequences test is similar to the standard Trial-Making Test (Letz 1991). In this test, the subject must touch a set of circles with numbers on the computer screen in numerical order as quickly as possible. Then the subject must touch circles with numbers and letters on the computer screen, alternating

Table 2. Comparison of health status at the beginning of the TOS epidemic between TOS patient participants and TOS patient nonparticipants: study of long-term neurologic outcomes of TOS, Madrid, Spain, 1999.

Characteristic	Patient participants	Nonparticipants
Age (mean ± SD)	44.9 ± 13.3	44.1 ± 13.9
Sex (%)		
Female	65.0	62.2
Male	35.0	37.8
Motor neuropathy (%)	27.5	19.5
Cramps (%)	43.8	32.9
Sensory neuropathy (%)	57.5	53.7
Myalgias (%)	88.8	89.0

All *p*-values were nonsignificant.

Table 3. Sociodemographic and other characteristics for TOS patients and referent population: study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

Variable	TOS patients	Referent group
Age, median (10th–90th percentiles)	50.5 (25.0–59.0)	48.0 (24.0–59.0)
BMI, median (10th–90th percentiles)	25.9 (9.6–30.8)	25.1 (20.5–30.7)
K-BIT score, median (10th–90th percentiles)	99.5 (82.5–119.5)	101.5 (85.5–115)
Sex, no. (%)		
Male	28 (35.0)	27 (34.2)
Female	52 (65.0)	52 (65.8)
Work situation,[a] no. (%)	61 (76.3)	60 (75.9)
Educational level,[b] no. (%)	27 (33.7)	19 (24.0)
Marital status,[c] no. (%)	56 (70.0)	55 (69.6)
Habits, no. (%)		
Alcohol	27 (33.7)	29 (36.7)
Current smokers	31 (38.7)	30 (38.0)
Drugs	3 (3.7)	1 (1.3)

[a]Percentage of active workers. [b]Percentage of people who are illiterate or who know how to read or write only. [c]Percentage of married people.

between numbers and letters (i.e., 1, A, 2, B, etc.). The preferred summary measures are the latency to complete the set of numbers (sequence A latency) and the numbers and letters (sequence B latency).

The auditory digit span test measures attention and short-term memory. It consists of auditory presentation of sequences of single digits with the participant required to press numbered keys on the computer screen in order to represent the sequence. Increasingly longer sequences are presented until the subject makes mistakes on two trials at a given span length. Then digit sequences are presented, and the subject must press the numbered keys in reverse order from their auditory presentation. The test continues until incorrect responses are given on two trials at a given span length. The longest sequences forward and backward answered correctly are the summary measures for this test.

The visual span test is a visual analog to the digit span test. Large blocks visible on the computer screen are highlighted in a temporal sequence. The subject must reproduce each sequence by touching the blocks on the screen. Longer sequences are presented until two errors are made at a given span length. A "backward" condition in which the subject must reproduce the sequence in reverse order is also administered. Patients were asked about their familiarity with video games, and self-reported effort [Tryhard; a categorical appraisal of the difficulty perceived when performing the test; range: 0 (no difficulty) to 4 (maximum difficulty)] in performing neurobehavioral tests in order to assess their dexterity as confounding variables.

The Programa Integrado de Exploracion Neuropsicologica [Integrated Program of Neuropsychologic Examination (PIEN); Peña-Casanova 1990] is a manual test to assess a learning task with delayed recall; the PIEN is used to evaluate a number of learning and memory parameters (acquisition, rate of learning, interference, and delayed recall). The vocabulary portion of the Kaufman Brief Intelligence Test (K-BIT), Spanish version (Kaufman and Kaufman 1996), was given to measure vocabulary ability. The number of correct items can be used as an index of native intellectual ability that is resistant to the effect of neurotoxicants, for "adjusting" the other neurobehavioral outcome variables in regression analyses.

All data for standing stability, heart rate variability, NES2, and NES3 were written directly to computer disk files. Special-purpose data summary programs reduced these raw data to produce summary measures for each test. The questionnaire and manually administered neurobehavioral testing data were entered into database files for analysis.

Statistical Methods

The frequencies of currently reported neurologic symptoms were stratified by case and referent group. Given that women have had a poorer prognosis than men (Abaitua et al. 1998; Posada de la Paz et al. 1999), the statistical analyses were focused first on the overall group and then stratified by sex. Median and 10th percentile/90th percentile were used on all examiner-administered manual, neuropsychologic, and heart rate variability tests. Associations between the case and referent groups and the neurobehavioral and neurophysiologic outcomes of interest were examined. The difference in median test scores between cases and referents was tested with nonparametric tests (Wilcoxon test). The severity of neurologic findings in TOS patients was assessed using the following criteria as a reference measure (gold standard): in those quantitative tests in which a higher score indicates better performance, we have considered a pathologic outcome for TOS patients to be values less than the 10th percentile of referent group values; in those tests in which a higher score indicates poorer performance, we have considered a pathologic outcome for TOS patients to be values greater than the 90th percentile of the referent group values.

Table 4. Causes for specific exclusions and number of participants who completed each test: study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

	TOS patients ($n = 80$)		Referent group ($n = 81$)	
Reason for exclusion	Excluded	Accepted	Excluded	Accepted
Age (< 18, > 65 years)	0	80	2	79
PNS				
Motor examinations (cast right hand, broken left wrist, torn long flexor right hand, surgery left wrist)	2	78	2	77
Sensory examinations	0	80	0	80
ANS				
Coding error, medication use that could interfere with testing (e.g., beta blockers, calcium antagonists, bronchodilators, antidepressants)	11	69	10	69
CNS				
NES2 test (visual problems)	4	76	2	77
NES3 test (functionally illiterate, visual problems)	6	74	6	73
Grooved pegboard (visual problems)	11	69	5	74

Table 5. Distribution of neurologic symptoms by sex in TOS patients and referent group, study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

Symptoms by sex	TOS patients	Referent group	OR (95% CI)	*p*-Value
Males				
CNS				
Sleep trouble	10	2	6.94 (1.53–31.40)	0.01
Headache	7	3	2.67 (0.62–11.40)	NS
Memory Loss	9	1	12.31 (2.00–75.76)	0.003
Poor coordination	1	0	3.00 (0.18–76.90)	NS
PNS				
Motor symptoms				
Myalgias	10	4	6.94 (1.54–31.40)	0.01
Myoclonias	3	0	7.55 (0.37–153.0)	NS
Muscle spasms	11	1	16.82 (1.98–142.0)	0.002
Strength loss	7	4	4.16 (0.84–20.66)	NS
Sensory symptoms				
Numbness	8	1	10.40 (1.62–66.71)	0.01
Paresthesias	12	2	9.37 (2.16–40.66)	0.003
Hypoesthesias	3	1	3.12 (0.32–29.50)	NS
Females				
CNS				
Sleep trouble	22	9	1.65 (0.73–3.69)	NS
Headache	27	13	3.24 (1.42–7.36)	0.005
Memory loss	21	11	2.52 (1.07–5.95)	0.03
Poor coordination	4	1	4.26 (0.46–39.54)	NS
PNS				
Motor symptoms				
Myalgias	25	9	4.44 (1.83–10.79)	0.001
Myoclonias	19	1	30.03 (6.77–133.16)	0.001
Muscle spasms	26	1	53.08 (6.79–414.8)	0.001
Strength loss	19	7	3.76 (1.41–10.05)	0.006
Sensory symptoms				
Numbness	27	5	10.15 (3.82–26.95)	0.001
Paresthesias	26	10	4.10 (1.73–9.86)	0.001
Hypoesthesias	13	4	4.00 (1.27–12.58)	0.020

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; NS, not significant.

Subsequently, stepwise backward elimination multiple linear regression models were fitted separately to each of the neurobehavioral test score variables to control for potentially confounding effects of important covariates of the neurologic and neurobehavioral outcomes in this population. The initial set of covariates for the PNS outcomes included age, sex, height, and body mass index (BMI). The set of potential covariates of CNS function were age, sex, education, K-BIT score, experience in using video games, and an index of self-reported effort (Tryhard) when performing the tests (both coded 1–4). The exposure group variable was forced into all the backward elimination stepwise regression models. Potential covariates were eliminated until only the variables related at the $p < 0.05$ level to the outcome variable remained in the model. Results of these analyses are presented in terms of the standardized regression coefficients of the variables remaining in the models. All statistical analyses were performed with SAS statistical software, version 6.12 for Windows (SAS Institute 1989).

Results

Of the 160 TOS patients for which telephone contact was attempted using the randomized list of TOS patients in Alcorcón, 13 did not meet the inclusion criteria and 67 refused or were otherwise unable to participate, for an overall participation rate of 54.4% (80 of 147) of eligible participants contacted (Table 1). We found no difference between TOS case participants and TOS patients who refused to participate in terms of neurologic symptoms at the time the epidemic began ("first years since the outbreak," checked with the REVCEN, the official TOS morbidity registry) (Table 2). Table 3 shows the sociodemographic characteristics of the TOS case patients and the referent group. No significant differences were found between the two groups in terms of age, sex, BMI, work status, educational level, or tobacco, alcohol, and drug consumption. Table 4 shows the number of participants in each group who were excluded from the final analyses for specific neurologic tests but who were included in all other tests analyzed. We excluded two of the original 81 referent group participants because they did not meet the age criteria. Thus, 79 participants were included as the final referent group.

Symptoms and neurologic examination. The percentage of some neurologic symptoms was significantly higher in women than in men in TOS patients: headache, 51.9% versus 25%; myoclonias, 38.5% versus 10.7%; and numbness, 51.9% versus 28.6%, respectively. We found statistically significant differences between the TOS patients and the referent group for myoclonias, muscle spasms, numbness, loss of strength, hypoesthesias, paresthesias, poor coordination, headache, trouble sleeping, and memory loss. After stratifying by sex, we found that the overall results were driven primarily by the effects in women. Table 5 shows the distribution of neurologic symptoms referred by the participants between TOS patients and the referent group stratified by sex. These differences between the TOS and referent groups were greater in women > 35 years of age except for trouble sleeping, which did not change when it was stratified for the same variables. For men, however, these differences disappeared for the following variables: headache, poor coordination, myoclonias, strength loss, and hypoesthesias.

Unlike reported neurologic symptoms, the standard clinical neurologic examinations made by experienced neurologists did not show differences between the TOS and referent groups except for an increase in pain in the upper limbs and diminished superficial sensation in the lower limbs, although five TOS patients did show a minor loss of strength against external resistance (scored as 4/5).

Quantitative neurologic examination. Table 6 shows the results of the specific quantitative neurologic tests. For the six measures of strength, between 28.2% and 35.9% of the TOS patients had a strength lower than the lowest 10th percentile of the referent group. Of the four measures of vibratory sensation, between 13.8% and 22.5% of all TOS patients had a vibratory threshold greater than the 90th percentile of the referent group in at least one of the variables measured. Among the tests used to assess cognitive function, we found that three of them showed that more than 20% of TOS patients were over the 90th percentile of the referent group: simple reaction time latency, sequence B latency, and digital symbol latency.

When the analysis was stratified by sex, most of these percentages were increased in female TOS patients and ranged from 38% to 48% for strength measurements, from 19.2% to 36.5% for vibratory sensation, and from 27.9% to 30.2% for the aforementioned cognitive tests.

When we analyzed the effect of age by sex, women between 35 and 55 years of age showed the poorest strength scores. In tests of sequence latency and digit symbol latency, used for assessment of attention, mental concentration, and coding difficulty, latencies greater than the 90th percentile of the referent group were found in 14% of all women and 27.9% of all women > 55 years of age. The simple reaction time increased with age. This percentage ran from 30.2% for all women to 41.7% for women > 55 years of age.

Table 7 shows the median scores for the neurologic and neurobehavioral outcomes in both the TOS and referent groups. In all

Table 6. Quantitative neurologic tests: percentage of all TOS patients, female TOS patients, and females in two age strata, who fall below the 10th percentile or above the 90th percentile compared with the reference group in the study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

		Females		
TOS patients	Both sexes	All females	> 35 to < 55 years	> 55 years
Motor strength evaluation				
Distal strength preferred hand	29.5	40.0	36.8	47.1
Distal strength nonpreferred hand	30.8	46.0	52.6	47.1
Lateral pinch preferred hand	28.2	42.0	52.6	47.1
Lateral pinch nonpreferred hand	34.6	42.0	57.9	41.2
Palmar pinch preferred hand	35.9	48.0	57.9	35.3
Palmar pinch nonpreferred hand	32.1	38.0	68.4	41.2
Grooved pegboard preferred hand	21.2	18.0	25.0	27.3
Grooved pegboard nonpreferred hand	19.7	21.0	25.0	27.3
Finger tapping nonpreferred hand	15.0	23.1	31.3	36.4
Finger tapping left/right	12.0	15.4	18.8	9.1
Hand–eye coordination	7.6	5.1	6.3	9.1
Vibratory sensation				
Preferred hand	18.8	26.9	10.5	36.8
Nonpreferred hand	22.5	36.5	31.6	63.2
Preferred foot	17.5	19.2	31.6	15.8
Nonpreferred foot	13.8	28.8	36.8	36.8
Standing steadiness				
Eyes open	11.3	19.2	10.5	21.1
Eyes closed	13.3	23.1	26.3	31.6
Cognitive				
Sequence A latency	10.0	14.0	11.8	16.7
Sequence B latency	25.4	27.9	0.0	16.7
Digital symbols latency	20.9	27.9	29.4	0.0
Auditory digit span forward	9.0	11.6	0.0	0.0
Auditory digit span backward	14.9	14	17.6	0.0
Visual span forward	14.9	0.0	0.0	0.0
Visual span backward	0.0	16.3	0.0	0.0
Simple reaction time	20.9	30.2	35.3	41.7

measures used, TOS patients performed more poorly than the referent group, although the results were not statistically significant in 13 of 27 tests. Statistically significant differences were found between the TOS patients and the referent group in the results of peripheral nerve function tests such as the median of the distal strength, lateral pinch and palmar pinch of the hands, and vibrotactile thresholds.

Electrocardiographic R–R intervals are somewhat variable at rest and more variable during deep breathing in normal individuals. Autonomic neuropathy can lead to reduced impact of deep breathing on R–R interval variability. The median coefficient of variation of R–R intervals at rest was 3.1% in both groups, whereas during deep breathing the median coefficient of variation was statistically significantly lower in the TOS group (5.25%) than in the referent group (7.3%, $p = 0.007$).

The results of the standing steadiness test, a quantitative analog to the clinical Romberg test, with eyes open and eyes closed was similar for both the TOS and referent groups. Results of tests of motor quickness and coordination (grooved pegboard, finger tapping, and hand–eye coordination) were also similar for both the referent and TOS groups.

TOS patients, however, had poorer results on five of the eight cognitive functions tested. Of the five cognitive function tests, the largest differences between the TOS group and the referent group were found for the sequence B test, the digit symbol test, and the auditory digit span test.

Table 8, like Table 7, shows the median scores for the neurologic and neurobehavioral outcomes in both the TOS and referent groups; however, in Table 8 the results are analyzed only for the female participants of both groups. These results show more dramatic differences than those of all subjects together.

Multivariate analysis. To control for potential confounding, all outcome variables and first-order interaction variables were analyzed by stepwise backward elimination multiple linear regression models. Table 9 shows the standardized regression coefficients from these models. Anxiety, depression, and PIEN score were introduced as independent variables in the models, although these variables did not remain in any of the final models, except for anxiety, which remained in the reverse auditory digit backward span model. In these models, TOS patients showed poorer performance than the referent group in five of the six variables used to measure distal strength. Age, sex, BMI, and the interaction variables sex–case and age–case were retained in the final model. Standing steadiness, with eyes open as well as with eyes closed, was not associated with illness even after adjusting for sex and BMI. Regardless of statistical significance, the estimated effect of being in the exposed group was positive for 9 of the 12 PNS outcomes analyzed. The total variance accounted for by the multiple regression models of PNS outcomes varied widely from an $R^2 = 0.10$ for standing steadiness with eyes open to an $R^2 = 0.71$ for distal strength of the dominant hand.

In the analysis of the ANS test results, independent variables for tobacco, alcohol, and drug use were entered initially, although none of these remained in the model.

Analysis of the cognitive testing, after controlling for covariates, showed a statistically significant relationship between poor performance on the sequence B test, the digit symbol test, the reverse auditory digit test, and simple reaction time test, and risk of being a TOS case patient. The K-BIT, which measures vocabulary ability, was an important covariate for all cognitive outcomes. Age, sex, familiarity with video games, and self-reported effort (Tryhard) in performing the tests, as well as some interaction variables such as age–K-BIT and K-BIT–Tryhard, were significantly related to some of the cognitive outcomes. R^2 varied between 0.20 and 0.70. No exposure group differences were statistically significant for tests of coordination.

Discussion

This study of TOS patients reports the first quantitative evidence of the existence of a neurologic deficit that has persisted for 18 years after the intoxication. These findings are very important because in all of the TOS case series published (Martin Alvarez et al. 2000; Philen and Posada 1993), as well as in the experience of the physicians who work with these patients, neurologic symptoms have been a major clinical complaint. However, in many patients it had not been possible to demonstrate the existence of real neurologic lesions because of lack of sensitivity of the clinical neurologic examination. Additionally, clinicians often decided against a muscle or nerve biopsy because no effective treatment is available. On some occasions TOS patients have been stigmatized with other diagnoses such as depression, anxiety syndrome, or neurosis.

We found that TOS-affected participants consistently reported more symptoms than a referent group matched by sex and age, a finding that has been suspected but not previously documented. Although the frequencies of neurologic symptoms in the TOS group were very high, no clinically relevant abnormalities were observed in the physical neurologic examinations performed by either

Table 7. Quantitative neurologic measures of TOS patients and reference subjects in the study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

	TOS patients	Referent group	
Neurologic test	Median (10th–90th percentiles)	Median (10th–90th percentiles)	*p*-Value
Motor			
Distal strength preferred hand	24.8 (10.7–45.3)	28.3 (18.3–46.0)	0.05
Distal strength nonpreferred hand	22.7 (8.3–44.2)	26.0 (18.0–43.0)	0.03
Lateral pinch preferred hand	7.2 (2.8–11.5)	8.0 (5.8–11.7)	0.05
Lateral pinch nonpreferred hand	6.3 (2.7–10.7)	7.3 (5.3–10.8)	0.03
Palmar pinch preferred hand	6.8 (2.8–11.2)	7.8 (5.7–11.2)	0.01
Palmar pinch nonpreferred hand	6.3 (2.7–10–7)	7.2 (5.2–10.2)	0.01
Finger tapping nonpreferred hand	122.5 (80.0–148.0)	123.0 (99.0–153.0)	NS
Finger tapping left/right	157.0 (103.0–217.0)	168.0 (118.0–225.0)	NS
Hand–eye coordination	2.3 (1.7–2.9)	2.3 (1.8–2.8)	NS
Grooved pegboard preferred hand	64.0 (51.0–87.0)	61.5 (52.0–76.0)	NS
Grooved pegboard nonpreferred hand	70.5 (55.0–100.0)	68.0 (58.0–87.0)	NS
Vibratory sensation			
Preferred hand	0.44 (0.11–0.83)	0.39 (0.05–0.64)	NS
Nonpreferred hand	0.37 (0.08–0.85)	0.27 (0.04–0.57)	0.004
Preferred foot	0.98 (0.62–1.65)	0.89 (0.53–1.51)	0.05
Nonpreferred foot	0.98 (0.56–1.72)	0.89 (0.54–1.56)	NS
Standing steadiness			
Eyes open	1.68 (1.39–2.01)	1.65 (1.47–1.89)	NS
Eyes closed	1.86 (1.59–2.39)	1.87 (1.60–2.34)	NS
Cognitive			
Sequence A latency	24.0 (16.5–39.5)	21.6 (15.3–35.9)	NS
Sequence B latency	48.2 (29.4–107)	39.4 (25.9–86.2)	0.002
Digital symbol latency	102.6 (74.5–180)	89.8 (72.6–137)	0.04
Auditory digit span forward	5.0 (4–7)	6.0 (4–7)	0.04
Auditory digit backward span	4.0 (2–5)	4.0 (3–6)	0.008
Visual span forward	5.0 (3–6)	5.0 (4–6)	0.04
Visual span backward	4.0 (3–5)	4.0 (3–6)	NS
Simple reaction time	285.0 (233.0–432.0)	276.6 (232.0–349.0)	NS
ANS			
CV of R–R (rest)	3.2 (1.6–6.3)	3.0 (1.8–6.6)	NS
CV of R–R (deep breathing)	5.45 (2.2–13.2)	7.0 (3.4–14.1)	0.02

Abbreviation: CV, coefficient of variation; NS, not significant.

of the two neurologists who examined the study participants.

In the present study, we used quantitative neurologic techniques originally developed to identify workers with neurologic lesions resulting from occupational exposures to assess neurologic signs and symptoms of a sample of TOS patients. These techniques have already been applied successfully in the study of other diseases and environmental exposures, such as EMS (Sullivan et al. 1996), epidemic neuropathy in Cuba (Cuba Neuropathy Field Investigation Team 1995), and people exposed to lead (Stokes et al. 1998). This is the first study of TOS patients to use quantitative neurologic techniques to study the differences between quantitative and objective neurologic measures and the relationship of these measures to reported symptoms. The results of this quantitative neurologic testing suggest that an additional evaluation of TOS patients beyond the standard clinical assessments may be needed to detect the adverse consequences of exposure.

In evaluating the results from the quantitative neurologic examinations, we used the 10th and 90th percentiles of each measure taken in the referent population to calculate the percentage of TOS patients who had scores that were less than or more than these thresholds as well as the comparison among medians of each test performed. The ANS tests showed no substantial differences between the TOS and referent groups except for a coefficient that measured the change in heart rate between resting and deep breathing, suggesting less autonomic reactivity in the TOS group. Most of the PNS tests showed significantly worse performance in the TOS group than in the referent group. The quantitative neurologic tests performed in this study demonstrated a clear motor and sensory deficit in TOS patients, most likely a result of the original neuropathy caused by TOS. Although some participants partially recovered from the original neuropathy, some residual deficit was still present and measurable. These sequelae were more important in women, showing a more severe motor deficit in the 35–55-year-old group and lessened vibratory sensation among older women of the TOS group. These findings are congruent with observations in the TOS cohort that, at the beginning of the epidemic, young women would have had a poor prognosis (Posada de la Paz et al. 1999). Although distal sensation loss is a frequent finding in older people, TOS-affected women showed poorer results than did the referent group adjusted by age.

In order to properly complete the standing steadiness test, it is necessary that the vestibular, vision, and proprioceptive systems and the central coordination of motor responses are not damaged. Considering that these systems are very sensitive, any neurologic disorder might have been detected. However, no significant differences were found.

The high proportion of CNS abnormalities observed among the TOS patients are the first sign of possible CNS lesions related to TOS. This is the first study in which a likely memory disorder and less response to stimulus have been quantified in these patients. Although some neuronal abnormalities, such as vacuolization, have been seen in the necropsies of some TOS patients, a CNS lesion was never clearly established (Ricoy et al. 1983). In addition, although 1% of the total cohort developed brain edema during the acute phase, and memory loss has been one of the major complaints of this cohort (Portera-Sanchez and Posada de la Paz 2000), actual CNS lesions have never been identified in TOS patients using an objective test. Although our study does not prove the existence of a CNS lesion, a careful follow-up of a group of patients should be done in order to rule out that possibility.

The Alcorcón locality was selected for this study primarily for logistical purposes; the neighborhood has a new, modern hospital that allowed us to use its facilities, and the area has a large enough population of TOS-affected people from which to sample. Past studies have not shown any major differences between the population of Alcorcón and other TOS-affected populations (Gomez et al. 1998).

Although the response rate was 54.4%, we did not find any significant differences between TOS patients who participated and TOS patients who refused to participate in terms of age, sex, or main features of the disease checked with the official morbidity registry (REVCEN) (Kilbourne et al. 1992). The referent group cannot be considered a real control group because our goal was not to carry out a case–control study but to obtain some reference data from people from the same locality who were not affected and to adjust these data by age and sex. (A referent case only uses the controls as a population reference pattern; it does not intend to estimate the relative risk but provides a normality pattern of such population from which cases have been recruited.) In our opinion, and despite the fact that the referent group does not come from a simple random sampling of the Alcorcón locality, the results could be biased. The absence of randomization could have selected a population subgroup more eager to collaborate for causes related to their health status. Adjustment was made using other variables such as age, sex, education level, and cognitive basal tests in order to reduce this potential bias.

Table 8. Quantitative neurologic measures of TOS patients and reference subjects in the study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

Neurologic test	TOS patients Median (10th–90th percentiles)	Referent group Median (10th–90th percentiles)	*p*-Value
Motor			
Distal strength preferred hand	19.5 (8.8–26.5)	25.0 (16.5–31.0)	0.0001
Distal strength nonpreferred hand	18.3 (6.0–25.0)	23.3 (17.2–29.0)	0.0001
Lateral pinch preferred hand	5.8 (2.3–8.4)	7.2 (5.4–8.3)	0.0003
Lateral pinch nonpreferred hand	5.1 (1.9–7.8)	6.7 (4.7–8.0)	0.0001
Palmar pinch preferred hand	5.4 (2.2–8.0)	7. (5.3–8.4)	0.0001
Palmar pinch nonpreferred hand	5.1 (2.1–7.0)	6.4 (5.0–7.7)	0.0002
Finger tapping nonpreferred hand	109.5 (73.0–137.0)	112.0 (98.5–148.0)	NS
Finger tapping left/right	138.0 (92.0–200.0)	159.5 (115.0–219.0)	0.01
Hand–eye coordination	2.4 (1.7–2.9)	2.4 (1.8–2.9)	NS
Grooved pegboard preferred hand	62.0 (51.0–87.0)	63.0 (53.0–76.0)	NS
Grooved pegboard nonpreferred hand	68.0 (57.0–98.0)	70.0 (58–87.0)	NS
Vibratory sensation			
Preferred hand	0.5 (0.2–0.8)	0.4 (0.1–0.6)	0.04
Nonpreferred hand	0.4 (0.1–0.8)	0.3 (0.01–0.5)	0.004
Preferred foot	1.0 (0.6–1.6)	0.9 (0.6–1.4)	0.02
Nonpreferred foot	1.0 (0.6–1.6)	0.9 (0.6–1.3)	0.02
Standing steadiness			
Eyes open	1.9 (1.6–2.5)	1.9 (1.5–2.2)	NS
Eyes closed	1.7 (1.4–2.1)	1.6 (1.5–1.9)	NS
Cognitive			
Sequence A latency	25.4 (17.6–39.9)	21.2 (15.3–35.9)	0.03
Sequence B latency	58.1 (34.7–108.4)	39.6 (25.8–93.0)	0.003
Digital symbol latency	107.2 (79.1–180)	86.5 (72.6–163.3)	0.01
Auditory digit span forward	5.0 (3–6)	6.0 (4–7)	0.005
Auditory digit span backward	4.0 (2–5)	4.0 (3–6)	0.02
Visual span forward	5.0 (3–6)	5.0 (3–6)	NS
Visual span backward	4.0 (3–5)	4.0 (4–6)	0.01
Simple reaction time	06.2 (238–472.4)	281.7 (236.6–361.0)	0.02
ANS			
CV of R–R (rest)	3.05 (1.6–6.3)	3.1 (1.8–6.6)	NS
CV of R–R (deep breathing)	5.25 (2.1–11.6)	7.3 (3.4–14.1)	0.007

Abbreviation: CV, coefficient of variation; NS, not significant.

Table 9. Standardized regression coefficients from stepwise regression models for neurologic and neurobehavioral outcomes: study of long-term neurologic outcomes of TOS patients, Madrid, Spain, 1999.

Dependent variable	TOS	Age	Sex	BMI	Education	Video games	Tryhard	K-BIT	Anxiety	Interaction variables[a]	R^2
PNS test											
Motor evaluation											
Distal strength preferred hand	0.35*	—	–0.19	—	—	—	—	—	—	1	0.71
Distal strength nonpreferred hand	–0.12*	—	–0.63	—	—	—	—	—	—	—	0.65
Lateral pinch preferred hand	–0.17*	–0.21	–0.69	0.16	—	—	—	—	—	—	0.58
Lateral pinch nonpreferred hand	0.35	0.33	–0.52	0.16	—	—	—	—	—	1	0.58
Palmar pinch preferred hand	–0.23**	–0.22	–0.65	—	—	—	—	—	—	—	0.56
Palmar pinch nonpreferred hand	–0.21**	–0.22	–0.67	0.12	—	—	—	—	—	—	0.57
Simple reaction time[b]	0.15*	0.29	0.27	—	—	—	—	—	—	—	0.20
Grooved pegboard preferred hand	0.07	2.31	–1.31	—	—	—	—	0.42	—	2	0.40
Grooved pegboard nonpreferred hand	0.06	0.32	–0.16	—	–0.22	—	—	0.72	—	1	0.36
Finger tapping nonpreferred hand	–0.05	–0.20	0.07	—	0.20	—	—	—	—	1	0.54
Finger tapping left/right	–0.06	–0.37	—	—	0.27	0.17	—	—	—	—	0.57
Hand–eye coordination	–0.08	0.36	0.17	—	0.23	—	—	–0.20	—	—	0.48
Standing steadiness											
Eyes closed[b]	0.01	0.01	—	–0.30	—	—	—	—	—	—	0.30
Eyes open[b]	–0.02	0.01	—	–0.02	—	—	—	—	—	—	0.10
Sensory evaluation											
Vibration threshold preferred hand[b]	–0.88*	0.49	0.13	–0.59	—	—	—	—	—	1	0.32
Vibration threshold nonpreferred hand[b]	–1.19*	0.39	—	–0.72	—	—	—	—	—	1	0.36
Vibration threshold preferred foot[b]	0.17**	1.19	0.68	—	—	—	—	—	—	1	0.35
Vibration threshold nonpreferred foot[b]	0.13*	0.61	—	—	—	—	—	—	—	—	0.31
Electrophysiological (ANS)											
CV of R–R interval (deep breathing)	–0.09	–0.62	—	—	—	—	—	—	—	—	0.40
CV of R–R interval (normal breathing)	0.10	–0.44	—	—	—	—	—	—	—	—	0.19
Cognitive (CNS)											
Sequence A latency[b]	0.08	2.18	—	—	—	—	—	0.52	—	1	0.46
Sequence B latency[b]	0.16**	1.78	—	—	—	—	—	0.15	—	1	0.63
Digital symbol latency[b]	0.94**	2.50	0.11	—	—	—	—	0.67	—	2	0.70
Auditory digit span forward	–0.08	—	—	—	—	0.20	—	0.48	—	—	0.34
Auditory digit span backward	–0.13*	–0.25	—	—	0.18	—	—	0.26	–0.15	—	0.41
Visual span forward	–0.13	–0.37	—	—	—	—	—	0.24	—	—	0.28
Visual span backward	–0.09	–0.50	—	—	—	—	–0.15	0.20	—	—	0.33

CV, coefficient of variation. Patients group was coded as 0 = referent group, 1 = TOS patients. Sex was coded as 0 = male, 1 = female.
[a]Number of first order interaction variables that remain in the model. [b]Scores inverted so that higher score indicates better performance. *$p < 0.05$; **$p < 0.01$.

Because of specific individual factors, such as recent hand trauma or surgery, a few patients were excluded from certain tests. We do not believe that small differences in the number of cases included in each examination contributed to any significant bias in the final result.

This and other TOS-related research will continue to provide a basis for future research in groups of people affected with similar diseases, such as EMS and other neurologic syndromes with symptoms that are hard to quantify or document. Although these tests may not be useful for follow-up or diagnosis for an individual patient, they can be used as a screening tool for a population of patients with the same disease, or as a tool for follow-up to measure the improvement or deterioration over time of neurologic signs and symptoms in a specific group.

In summary, the TOS epidemic is not only an informative episode of environmental illness in modern medicine that merits follow-up of all its aspects, including etiology, clinical evolution, chemical toxicology, and pathogenesis, but it is also an episode from which researchers will continue to learn many things that will be applicable to similar problems in the future.

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