Effects of Sarin on the Nervous System in Rescue Team Staff Members and Police Officers 3 Years after the Tokyo Subway Sarin Attack

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Although the clinical manifestations of acute sarin poisoning have been reported in detail, no comprehensive study of the chronic physical and psychiatric effects of acute sarin poisoning has been carried out. To clarify the chronic effects of sarin on the nervous system, a cross-sectional epidemiologic study was conducted 3 years after the Tokyo subway sarin attack. Subjects consisted of the rescue team staff members and police officers who had worked at the disaster site. Subjects consisted of 56 male exposed subjects and 52 referent subjects matched for age and occupation. A neurobehavioral test, stabilometry, and measurement of vibration perception thresholds were performed, as well as psychometric tests to assess traumatic stress symptoms. The exposed group performed less well in the backward digit span test than the referent group in a dose–effect manner. This result was the same after controlling for possible confounding factors and was independent of traumatic stress symptoms. In other tests of memory function, except for the Benton visual retention test (mean correct answers), effects related to exposure were also suggested, although they were not statistically significant. In contrast, the dose–effect relationships observed in the neurobehavioral tests (psychomotor function) were unclear. None of the stabilometry and vibration perception threshold parameters had any relation to exposure. Our findings suggest the chronic decline of memory function 2 years and 10 months to 3 years and 9 months after exposure to sarin in the Tokyo subway attack, and further study is needed. *Key words*: **cross-sectional study, neurotoxicity, police officers, rescue workers, sarin.** *Environ Health Perspect* **109:1169–1173 (2001). [Online 6 November 2001]**
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On 20 March 1995, more than 5,500 people required emergency medical care after a sarin attack in the subways of Tokyo, and 12 people were killed. Although there was a similar sarin attack in Matsumoto City, Nagano Prefecture, Japan, in 1994, far more people suffered from poisoning in the subway sarin disaster in Tokyo than in the Matsumoto sarin attack.

Sarin is an organophosphate cholinesterase inhibitor and has been used as a strong military nerve gas. Recent reports suggest, however, that victims in the Tokyo subway sarin attack were exposed not only to sarin, but also to other by-products generated during sarin synthesis (*1,2*). Although the clinical manifestations of acute sarin poisoning have been reported in detail (*3–9*), no comprehensive study of the chronic physical and psychiatric effects of acute sarin poisoning has been carried out. Therefore, an epidemiologic study is needed to investigate the chronic effects of sarin poisoning. However, for the results of such an epidemiologic study to be valid, it must include subjects with homologous backgrounds. Thus, subway passengers who were victims of the disaster are inappropriate for the study because they are so varied in their backgrounds with regard to occupation, socioeconomic status, and educational level.

The rescue team members and police officers who were dispatched to the disaster were also exposed to sarin, primarily or secondarily. Therefore, to clarify the chronic physical and psychiatric effects of sarin, a cross-sectional epidemiologic study was conducted 2 years and 10 months to 3 years and 9 months after the sarin attack on the rescue team staff members and police officers involved in the disaster. In this paper we present the chronic effects of sarin poisoning on the central nervous system, on equilibrium, and on vibratory sensations in relation to traumatic stress symptoms.

Materials and Methods

Study design and study subjects. Fifty-seven study subjects were exposed to sarin, including 27 male rescue team staff members of the Tokyo Fire Department and 30 police officers of the Metropolitan Police Department. In each office of each department, rough matching by age took place, and 52 subjects without exposure, including 29 male rescue team staff members and 23 police officers were selected. After excluding one subject with amnesia not related to sarin exposure, the study population used for analysis consisted of 56 exposed subjects (exposed group) and 52 referent subjects (referent group). Written, informed consent was obtained from all subjects after fully explaining the study procedures.

To assess the dose–effect relationship, it was desirable to divide the subjects into groups according to their level of exposure, creating a high-exposed and low-exposed group. Because it was impossible to exactly estimate the exposure level of each subject, we assigned the subjects who had been hospitalized immediately after poisoning to a high-exposed group, and those who attended hospitals as outpatients to a low-exposed group, based on the description in the self-administered questionnaire. We checked the self-administered questionnaire, excluded two subjects who did not provide any information about their hospitalization, and assigned 25 subjects to the high-exposed group and 29 to the low-exposed group. Further, we classified the high-exposed subjects into two groups, namely, those who lost consciousness or suffered from dyspnea immediately after poisoning as a possible hypoxia-positive group, and the remaining as a possible hypoxia-negative group.

Information regarding age, height, weight, smoking status, alcohol consumption, and the location and nature of their work at the incident was obtained from the same self-administered questionnaire. Smoking status was assessed by multiplying packs per day by smoking years (pack-years). The amount of alcohol consumption during the course of a week was calculated in terms of the Japanese scale, gou (equal to about 23 g ethanol). Educational history was surveyed through office records. Table 1 shows the characteristics of the study subjects.

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The neurobehavioral test was carried out by our research group, as were stabilometry and vibration perception threshold determinations, at four offices of the Tokyo Fire Department and the Metropolitan Police Department without knowledge of information regarding exposure. There were no subjects with a present illness or past histories of disease affecting the central nervous system. Two subjects with low back pain and a past history of fracture of auditory ossicles, respectively, were excluded from the analysis for stabilometry.

Neurobehavioral tests. The neurobehavioral tests were performed to evaluate the chronic effects of sarin on the central nervous system. Because of time limitations, it was impossible to conduct the full neurobehavioral test battery recommended by the World Health Organization. We therefore selected the five neurobehavioral test items listed below. The items selected for assessing psychomotor function were finger tapping, simple reaction time, and choice reaction time. The items selected for checking memory function were digit span and the Benton visual retention test. Personal computer programs for the test items were written by one of the authors (K.O.). Before measurement, each examinee was given the opportunity to familiarize himself with the test procedures. These tests are described below.

The finger tapping test requires the subject to press a button as fast as possible with both the dominant and the nondominant hand. The median value of the tapping intervals was used as representative for each examinee.

In the simple reaction time test, the subject was required to press the button whenever a figure appeared on a monitor in a series of 20 trials of random-length intervals. The median value of the reaction times was used as the summary measure for each examinee. For the choice reaction time test, the subject was asked to memorize a basic pattern displayed on a screen for 5 sec. The subject was then required to judge whether the currently displayed pattern was the same as the basic pattern and to press an appropriate key according to his judgment as quickly as possible. In the choice reaction time, the median value of the reaction times for correct answers was used.

In the digit span test, the subject was asked to memorize a series of digits displayed on the screen at 1-sec intervals and to enter the digits into the computer in the order of their display within 10 sec. In the next session, the subject was asked to reproduce the digits in the reverse of the order displayed. The maximal digit number of the correct answer in both forward and backward digit span tests was used for analysis.

For the Benton visual retention test, the subject was asked to memorize a figure displayed on the screen for 10 sec. He was allowed to retain the memory for 15 sec, then he was asked to reproduce the figure on a sheet of paper within 10 sec. This session was repeated five times, and each time a different figure was displayed. One trained person without any knowledge of exposure status calculated the rate of correct answers and the number of errors.

Stabilometry. To assess the chronic effects of sarin on equilibrium, stabilometry was performed using the strain-gauge-type force platform (Gravicorder GS-3000; ANIMA, Tokyo, Japan) at a sampling frequency of 20 Hz, first with the subjects' eyes open, followed by testing with their eyes closed for 60 sec. The subjects were asked to watch a small, red circle 3 m away from where they were standing in a quiet, lighted room with a flat, hard floor. Before the test,

Table 1. Characteristics of the study subjects.

	Exposed						
	High (n = 25)		Low (n = 29)		Referents (n = 52)		
Characteristic	Mean	SD	Mean	SD	Mean	SD	p-Value[a]
Age (years)	43.8	9.9	44.7	9.3	42.7	9.8	0.65
Height (cm)	167.4	5.4	171.2	5.3	170.0	6.0	0.05
Body weight (kg)	66.0	7.1	72.4	8.4	69.8	11.0	0.05
Drinker (%)	84.0		89.7		88.5		0.80
Smoker (%)	56.0		55.2		58.8		0.94
Educational level (% college or higher)	33.3		20.7		35.3		0.38

Values shown are mean ± SD except where indicated.
[a]p-Value for analysis of variance or chi-square test.

Table 2. Results of neurobehavioral tests of psychomotor function, stabilometry, vibration perception thresholds, and psychometric test.

	Exposed				Referents	
	High (n = 25)		Low (n = 29)		(n = 52)	
	Mean	SD	Mean	SD	Mean	SD
Neurobehavioral test (psychomotor function)						
Tapping (dominant; msec)[a]	132.7	1.2**,#	114.3	1.1	120.7	1.2
Tapping (nondominant; msec)[a]	149.4	1.2	130.3	1.2	137.0	1.2
Simple reaction time (msec)[a]	255.5	1.2	242.1	1.1	246.9	1.1
Choice reaction time (msec)[a]	607.7	1.3	558.6	1.2	591.7	1.3
Stabilometry (eyes open)						
Total length (cm)[a]	84.3	1.4	96.7	1.2*,**,#	83.5	1.2
X length (cm)[a]	58.2	1.4	68.3	1.2*,**,#	57.3	1.2
Y length (cm)[a]	48.6	1.4	53.6	1.3	48.3	1.3
Sway area (cm^2)[a]	3.4	2.0	3.7	1.4	3.4	1.5
Stabilometry (eyes closed)						
Total length (cm)[a]	111.7	1.4	137.1	1.3*	114.5	1.3
X length (cm)[a]	75.2	1.4	91.6	1.4*	76.3	1.4
Y length (cm)[a]	66.3	1.5	81.4	1.4*	68.5	1.3
Sway area (cm^2)[a]	4.1	2.0	4.7	1.6	4.4	1.5
Vibration perception thresholds						
Right index finger (dB)						
63 Hz	3.8	7.1	4.1	4.7	3.0	6.0
125 Hz	–1.5	7.4	–1.6	5.8	–2.1	5.9
250 Hz	3.2	9.1	4.0	5.8	2.2	7.1
Right middle finger (dB)						
63 Hz	4.4	7.4	3.4	7.2	1.4	7.4
125 Hz	–1.3	5.7	–1.6	7.1	–2.7	6.9
250 Hz	4.5	7.8	3.3	5.4	2.5	8.6
Left index finger (dB)						
63 Hz	4.9	5.5	2.6	6.4	2.0	7.5
125 Hz	–0.9	6.2	–3.6	6.3	–3.5	7.0
250 Hz	2.8	7.4	1.2	5.6	0.8	8.3
Left middle finger (dB)						
63 Hz	1.8	6.1	2.9	7.0	0.6	8.9
125 Hz	–2.6	6.9	–2.4	6.1	–2.3	7.6
250 Hz	2.0	7.4	0.9	6.3	1.3	9.5
Psychometric test						
IES score	13.3	14.2	12.0	11.9	8.0	12.5
GHQ score	4.4	5.6	3.3	2.1	2.8	3.6

[a]Geometric mean and GSD. *$p < 0.05$ in Student's t-test or Welch's method compared to referents. **$p < 0.05$ for variable of group (dummy) in multiple regression analysis; the IES score was included as psychometric variable. #$p < 0.05$ for variable of group (dummy) in multiple regression analysis; the GHQ score was included as psychometric variable instead of the IES score.

care was taken to ensure that the platform was resting level on the floor.

The following body-sway parameters were used in this study: the total sway length of the center of foot pressure during the 60-sec measurement (total length), sway length in the medio-lateral (*X* length) and anterior-posterior (*Y* length) directions, and the area enclosed within the envelope of the outer perimeter of the *x-y* plot of the center of foot pressure (sway area).

Vibration perception thresholds. The vibration perception thresholds at the index and middle fingers bilaterally were measured at 63, 125, and 250 Hz, with a vibration sensation meter (AU-02B; Rion Co., Tokyo, Japan). Each subject was asked to place one fingertip on a 15-mm diameter plate vibrating at 65, 125, and 250 Hz. The investigator gradually increased the intensity of vibration at each frequency until the subject felt the vibration sensation. The threshold for each frequency at each finger was displayed in decibels.

Psychometric tests. Previous studies have determined that disaster workers such as firefighters (*10*) and police officers (*11*) are at risk of duty-related psychologic trauma. Therefore, we assessed traumatic stress symptoms of the subjects using the Impact of Event Scale (IES). A 15-item self-rating scale, the IES was developed by Horowitz et al. (*12*). Many studies using the IES have described its usefulness in the measurement of psychologic stress after traumatic events (*13*), and the reliability and validity of the Japanese-language version of the IES have been established (*14*). We also used the 30-item General Health Questionnaire (GHQ-30) (*15*) for evaluating general mental health. The Japanese-language version of the GHQ has also been well-validated (*16*).

Statistics. After appropriate transformation to obtain a normal distribution, mean values from the neurobehavioral tests (psychomotor function), and psychometric tests, as well as data from the stabilometry and vibration perception threshold determinations, were compared by the Student's *t*-test or Welch's method between the high-exposed and referent groups and between the low-exposed and referent groups, respectively. A nonparametric method, the Wilcoxon rank-sum test, was used for the values of memory function in the neurobehavioral test due to the discrete variables.

To control for possible confounding factors, we applied multiple regression analysis for the continuous variables and multiple logistic regression analysis for the discrete variables. In the multiple logistic analysis, cut-off points yielding dichotomous categories for dependent variables were set at median values. The confounding variables included in the model were age, height, weight, alcohol consumption (gou/week), smoking status (pack-years), and psychometric variables (IES score or GHQ score) for the stabilometry and the vibration perception thresholds; and age, educational level (high school, college, or higher), alcohol consumption, smoking status, and psychometric variables for the neurobehavioral test. All statistical analysis was performed using SAS software (SAS Institute, Cary NC, USA).

To control confounding, we excluded from the study 15 staff members (7 exposed, 8 referent) of the Identification Section in the Metropolitan Police Department who were routinely exposed to various other chemicals such as solvents and reagents at work. In addition, when appropriate, comparisons between possible hypoxia-positive and possible hypoxia-negative were made.

Results

Results of the neurobehavioral test of psychomotor function, stabilometry, vibration perception thresholds, and the psychometric test are shown in Table 2. In the neurobehavioral test of psychomotor function, the adjusted tapping interval for the dominant hand in the high-exposed group was larger than that in the referent group. For stabilometry, total length, and *X* length with eyes open in the low-exposed group were significantly larger than those in the referent group, even after adjustment. However, no dose–effect relationship was observed. None of the parameters for the vibration perception thresholds had any relation to exposure. Although no significant differences were found, the IES and GHQ scores did increase in a dose-dependent manner.

Table 3 shows the results of neurobehavioral tests of memory function. The maximal digit number in the backward digit span test in the high-exposed group was lower than that in the referent group, with marginal significance, and a dose–effect relationship was found between the maximal digit number in the backward digit span test and exposure. In the multiple logistic regression analysis, the prevalence of low performers in the backward digit span test was significantly higher in the high-exposed group than in the referent group (Table 4). The distribution of maximal digit numbers in the backward digit span test in each group is shown in Figure 1. In the analysis after excluding the staff members of the Identification Section, only the maximal digit number in the backward digit span test in the high-exposed group was lower than that in the referent group (Table 5). Table 6 shows the results of the neurobehavioral test with special reference to possible hypoxia. None of the neurobehavioral test items showed any relation to possible hypoxia.

Table 3. Results of neurobehavioral tests of memory function.

	Exposed				Referents	
	High (*n* = 25)		Low (*n* = 29)		(*n* = 52)	
Neurobehavioral test (memory)	Mean	SD	Mean	SD	Mean	SD
Forward digit span (maximal digit number)	6.12	1.51	6.52	1.43	6.38	1.48
Backward digit span (maximal digit number)	4.24	0.72*	4.69	1.37	5.00	1.71
Benton visual retention						
Mean correct answers	2.76	1.54	2.69	1.69	2.71	1.55
Mean errors	3.60	3.12	3.48	3.15	3.38	2.91

*$p = 0.07$ in Wilcoxon rank-sum test compared to referent group.

Table 4. Results of multiple logistic regression for neurobehavioral tests of memory function.[a]

		Exposed				Referents	
		High (*n* = 25)		Low (*n* = 29)		(*n* = 52)	
	Cut-off point	Prevalence (%)	Adj OR (95% CI)	Prevalence (%)	Adj OR (95% CI)	Prevalence (%)	Adj OR (95% CI)
Forward digit span							
Maximal digit number	≤ 6	60.0	1.15 (0.40–3.34)	51.7	0.73 (0.27–1.94)	57.7	1.00
Backward digit span							
Maximal digit number	≤ 4	68.0	3.19 (1.06–10.38)	51.7	1.17 (0.42–3.23)	46.2	1.00
Benton visual retention							
Mean correct answers (*n*)	≤ 3	60.0	0.52 (0.13–2.03)	65.5	0.54 (0.14–1.97)	63.5	1.00
Mean errors (*n*)	≥ 3	56.0	1.29 (0.41–4.08)	55.2	1.05 (0.36–3.05)	50.0	1.00

Abbreviations: CI, 95% confidence interval; Adj OR, adjusted odds ratio.
[a]Independent variables are group (dummy), age, educational level (high school, college, or higher), alcohol consumption (gou/week), smoking status (pack-years), and IES score.

Discussion

Our findings show that the exposed group performed less well in the backward digit span test than the referent group, in a dose–effect manner. This result was the same after controlling for possible confounding factors in the multiple logistic analysis and was independent of the IES score. In other tests of memory function, except for the Benton visual retention test (mean correct answers), effects related to exposure were also suggested, although they were not statistically significant. Thus, a dose–effect relationship and consistency were observed to infer the causal relationship between exposure to sarin and memory disturbance.

These findings are consistent with those of previous studies demonstrating disorders in the central nervous system in subjects exposed to sarin, as revealed by the persistence of an abnormal electroencephalogram (*17,18*) or an abnormal evoked potential (*19*). In contrast to our results, however, Yokoyama et al. (*20*) performed several neurobehavioral examinations on victims of the Tokyo subway sarin incident and observed no abnormalities in the digit span test. Because the results of Yokoyama et al. (*20*) were based on a rather smaller number of subjects (18 sarin cases and 15 controls) and because the test itself was performed in a different manner from ours, a simple comparison is meaningless. Nakajima et al. (*5*) conducted health examinations and a questionnaire survey in 52 rescue team members exposed to sarin in the Matsumoto sarin incident and reported that the symptoms of all the rescuers had disappeared 1 year after the incident. However, they did not evaluate subclinical conditions of subjects. Although there have been no comprehensive studies of the effects of sarin poisoning on the central nervous system, epidemiologic studies on organophosphate pesticide intoxication can provide us with valuable information. Rosenstock et al. (*21*) reported significant differences between subjects exposed to organophosphate pesticide and age-matched controls in the digit span test and the Benton retention test, but no significant difference between the two in tapping and simple reaction tests, results that are in good agreement with ours. Thus, epidemiologic coherence suggests causality between the sarin attack and memory disturbance.

In contrast, the mechanism of memory disturbance due to sarin remains unclear. As cholinesterase activity will recover to normal levels in approximately 3 months, the memory disturbance observed in the present study may have been caused by unknown mechanisms other than cholinesterase inhibition. Murata et al. (*19*) suggested that abnormal event-related potentials which were detected in subjects exposed to sarin may imply a consequence of lasting hippocampal pathology induced by sarin. According to an interesting recent study using the patch-clamp technique, sarin appears to inhibit the evoked release of γ-aminobutyric acid at low concentrations in rat hippocampal neurons, which are believed to be closely associated with memory function (*22,23*).

Contrary to the results of the neurobehavioral tests of memory function in the present study, the dose–effect relationships observed in the neurobehavioral tests of psychomotor function were unclear. None of the stabilometry and vibration perception

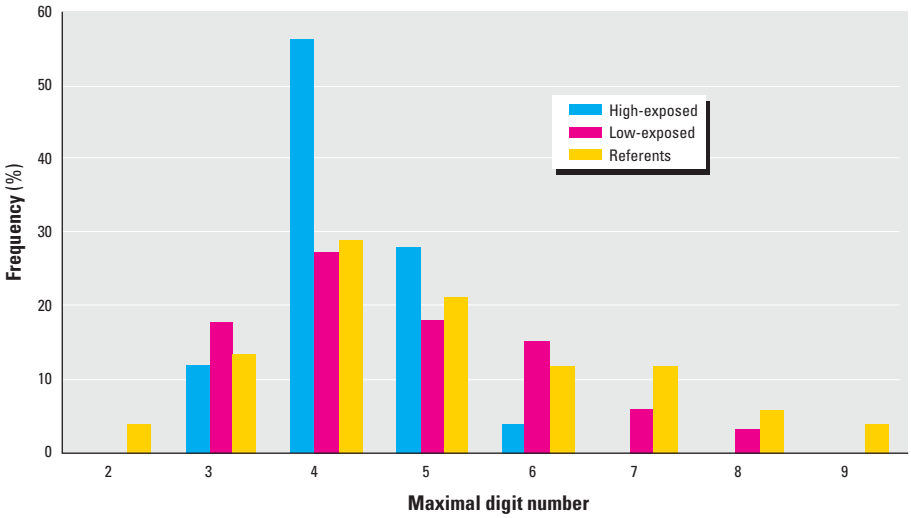

Figure 1. Distribution of maximal digit number in backward digit span test.

Table 5. Results of neurobehavioral tests after excluding the staff of the Identification Section.

	Exposed				Referents	
	High (n = 25)		Low (n = 22)		(n = 44)	
	Mean	SD	Mean	SD	Mean	SD
Tapping[a]						
Dominant (msec)	132.7	1.2	114.9	1.2	124.5	1.2
Nondominant (msec)	149.4	1.2	133.6	1.2	139.7	1.2
Reaction time[a]						
Simple (msec)	255.5	1.2	238.0	1.2	243.5	1.1
Choice (msec)	606.7	1.3	565.8	1.3	593.3	1.3
Digit span						
Forward (maximal digit number)	6.12	1.51	6.50	1.50	6.48	1.47
Backward (maximal digit number)	4.24	0.72*	4.64	1.43	5.16	1.74
Benton visual retention						
Mean correct answers	2.76	1.54	2.45	1.65	2.75	1.57
Mean errors	3.60	3.12	3.73	3.07	3.39	2.98

[a]Geometric mean and GSD. *$p < 0.05$ in Wilcoxon rank-sum test compared to referent groups.

Table 6. Results of neurobehavioral tests with special reference to possible hypoxia.

	Possible hypoxia positive (n = 10)		Possible hypoxia negative (n = 15)		
	Mean	SD	Mean	SD	p Value[a]
Tapping[b]					
Dominant (msec)	128.3	1.2	136.1	1.2	0.44
Nondominant (msec)	140.2	1.3	156.0	1.2	0.26
Reaction time[b]					
Simple (msec)	271.0	1.2	249.5	1.1	0.24
Choice (msec)	661.9	1.2	582.4	1.3	0.18
Digit span					
Forward (maximal digit number)	6.20	1.48	6.07	1.58	0.80
Backward (maximal digit number)	4.50	0.53	4.07	0.80	0.09
Benton visual retention					
Mean correct answers	2.40	1.51	3.00	1.56	0.28
Mean errors	4.10	3.18	3.27	3.15	0.36

[a]p-Value in Student's t-test or Welch's method or Wilcoxon rank-sum test between possible hypoxia positive and possible hypoxia negative. [b]Geometric mean and GSD.

threshold parameters had any relation to exposure.

This study has several limitations. First, it was impossible to estimate the exact exposure level. To assess the dose–effect relationship, we initially divided the subjects into high- and low-exposed groups according to the first-measured cholinesterase levels. However, we discarded this criterion for the following reasons: *a*) the interval between exposure and the measurement of cholinesterase activity varied from one subject to another; *b*) the measurement of serum cholinesterase activities were different among the hospitals; and *c*) it was impossible to obtain the serum cholinesterase level of each subject before the exposure. Thus, we assigned the exposed subjects according to their history of hospitalization. Second, among police officers, the persons from the Identification Section might have been exposed to chemicals such as solvents and test reagents. In this study we excluded 15 persons from the Identification Section, and the results were the same. Third, it is debatable whether the effects on the central nervous system observed in this study were truly caused by the direct action of sarin. They might rather have appeared as secondary effects due to hypoxia resulting from coma and dyspnea. To assess this hypothesis, we further divided the hospitalized patients into two groups according to the presence of possible hypoxia and compared their test results between the two groups; no significant difference was found between these two groups. We must also consider the involvement of psychiatric factors not represented by the IES score. In addition to the IES, which is specific for traumatic stress symptoms, we used the GHQ-30 as an instrument for evaluating the general mental health state of the subjects. The result was the same, even after adjustment for the GHQ score. It is possible, however, that certain psychiatric factors that could not be detected even by the evaluation based on the IES and GHQ scores were involved in the findings of this study. As such, there remains room for further investigation.

In conclusion, we observed the chronic decline of memory function in rescue team staff members and police officers 2 years and 10 months to 3 years and 9 months after exposure to sarin in the Tokyo subway sarin attack. This finding was independent of traumatic stress symptoms. However, it is necessary to determine whether the memory disturbance observed in this study is truly caused by the direct neurotoxicity of sarin, a determination that should be made based on further study and a body of sound evidence.

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