ELSEVIER

Journal of the Neurological Sciences 249 (2006) 76 – 85

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Sarin experiences in Japan: Acute toxicity and long-term effects

N. Yanagisawa [a,*], H. Morita [b], T. Nakajima [c]

[a] *Kanto Rosai Hospital, 1-1, Kizukisumiyoshicho, Nakahara-ku, Kawasaki, 211-8510, Japan*
[b] *Department of Medicine (Neurology), Shinshu University School of Medicine, Matsumoto, Japan*
[c] *Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Available online 7 September 2006

Abstract

Two terrorist attacks with the nerve agent Sarin affected citizens in Matsumoto and Tokyo, Japan in 1994 and 1995, killing 19 and injuring more the 6000. Sarin, a very potent organophosphate nerve agent, inhibits acetylcholinesterase (AchE) activity within the central, peripheral, and autonomic nervous systems. Acute and long-term Sarin effects upon humans were well documented in these two events.

Sarin gas inhalation caused instantaneous death by respiratory arrest in 4 victims in Matsumoto. In Tokyo, two died in station yards and another ten victims died in hospitals within a few hours to 3 months after poisoning.

Six victims with serum ChE below 20% of the lowest normal were resuscitated from cardiopulmonary arrest (CPA) or coma with generalized convulsion. Five recovered completely and one remained in vegetative state due to anoxic brain damage. EEG abnormalities persisted for up to 5 years.

Miosis and copious secretions from the respiratory and GI tracts (muscarinic effects) were common in severely to slightly affected victims. Weakness and twitches of muscles (nicotinic effects) appeared in severely affected victims. Neuropathy and ataxia were observed in small number (less than 10%) of victims, which findings disappeared between 3 days and 3 months. Leukocytosis and high serum CK levels were common. Hyperglycemia, ketonuria, low serum triglyceride, hypopotassemia were observed in severely affected victims, which abnormalities were attributed to damage of the adrenal medulla. Oximes, atropine sulphate, diazepam and ample intravenous infusion were effective treatments. Pralidoxime iodide IV reversed cholinesterase and symptoms quickly even if administered 6 h after exposure.

Post Traumatic Stress Disorder (PTSD) was less than 8% after 5 years. However, psychological symptoms continue in victims of both incidents.

In summary, both potent toxicity and quick recovery from critical ill conditions were prominent features. Conventional therapies proved effective in Sarin incidents in Japan.

Keywords: Sarin poisoning; Terrorism; Cause of death; Muscarinic effects; Cholinesterase activity; Psychological; After effects; PTSD

1. Introduction

Terrorists of a cult named "Aum Supreme Truth" attacked citizens with the nerve agent Sarin in 1994 in Matsumoto, and in 1995 in Tokyo, Japan. "Aum Supreme Truth" was founded in 1987 based on Buddhism, Yoga and Taoism. Cult members were predominately from young generations. The cult manufactured nerve agents Sarin and VX and biological weapons for countermeasures to its societal enemies, especially the police and other governmental agencies. The target of Sarin attack in Matsumoto was the district court; in Tokyo, the subway and the National Police Agency at Kasumigaseki-Sarin is an organophosphorous compound (methylphosphonofluoridic acid L-methylethyl ester), developed in 1938 as a chemical weapon. It is a potent cholinesterase inhibitor acting on the brain as well as somatic and autonomic nervous systems. LD_{50} in vapor form is 100 mg-min/m^3.

The first attack occurred in summer at midnight in a residential area. Nearly 600 people were poisoned with 7 deaths and 56 hospitalized victims. In the second attack, Sarin was released in several subway cars on different lines

* Corresponding author. Tel.: +81 44 411 3131; fax: +81 44 433 3150/435 5000.
E-mail address: yanagisawa@kantoh.rofuku.go.jp (N. Yanagisawa).

0022-510X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2006.06.007

leading to the government office center in Tokyo during a Monday morning rush hour. Twelve deaths and 5,500 exposures occurred.

The clinical states of the dead and injured victims, responses to various therapies, physical and psychological sequelae were recorded in both incidents with follow for up to 10 years. Because these were the first worldwide incidents with mass casualties caused by the nerve agent Sarin, it is important to describe the various aspects of the human toxicity. Because the two incidents occurred in different situations, rescue activities, the commitment of local administrations and follow up activities differed. Therefore, the events and outcomes are described separately.

2. The Matsumoto incident

At about 10:30 PM, June 27, 1994 in a quiet residential area of Matsumoto. 12 l of 70% Sarin solution were released within 10 min using a heater for evaporation and a motor vehicle's fan for dispensing the gas. Matsumoto is a city of 200,000 located in the central highlands of Japan.

The first emergency call arrived at 11:09 PM from a house located 20 meters from the presumed site of emission. Thereafter, ambulances transported injured people to 6 hospitals until 4:14 AM the 28th of June. Five victims were found dead before 0:15 am, on the 28th of June in two apartment buildings located 40 to 60 meters from the emission site. Three others were transported to hospitals in cardiopulmonary arrest. Of those, two died and one survived in persistent vegetative state due to anoxic encephalopathy. Casualties were: 7 dead, 56 admitted to hospitals; 208 who visited outpatient clinics; and 277 with symptoms but who did not seek medical attention.

Isopropyl methyl phosphoric acid and methyl phosphoric acid, the hydrolysis products of Sarin, were detected in body fluids in all seven dead people and in samples collected from soil, water and clothing near the emission site.

Shortly after the incident, a liaison committee and a regional comprehensive medical council was convened to investigate the event and to assess the health and patient care needed by residents. Representatives included: the city government, the local hospital, the Shinshu University School of Medicine, and doctors, dentists, pharmacists. The physical and psychological outcomes of the event from its acute phases to 10 years later were assessed.

Data recorded include: (1) clinical observations and laboratory findings of the severely injured or dead people; (2) subjective symptoms, clinical signs, responses to treatment of the severely to slightly injured people in the acute phase and for 3 weeks subsequently; (3) long-term neurobehavioral sequelae of casualties treated to Sarin poisoning. Results include health checks and questionnaire surveys of area resident and possible casualties at 3 months and up to 10 years later.

2.1. Clinical observations

2.1.1. Dead or critically injured subjects

All five people found dead in 2 apartments exhibited marked miosis. Circumstances suggested instantaneous deaths with signs of convulsions including oral frothing and opisthotonic posture. Two other people arrived at hospitals in cardiopulmonary arrest and died within 4 h. Another victim arrived at a hospital in cardiopulmonary arrest. After resuscitation, generalized seizures, muscular twitches and marked miosis occurred. This person survived in a persistent vegetative state due to anoxic encephalopathy [14,27,32,33].

Other severely affected subjects with loss of consciousness and generalized seizures recovered promptly after treatment with atropine sulphate, benzodiazepines, intravenous fluids and other systematic therapies. In general, muscarinic symptoms were resistant to treatment. Atropine sulphate was used in large amounts.

2.1.2. Severely, moderately and slightly affected individuals

Three weeks later, a community based questionnaire surveyed all inhabitants (2052 people) residing in an area within 1,050 and 850 meters of the Sarin release [18,33].

Affected subjects were classified into three groups: subjects admitted to hospital were classified as *severely affected*; subjects who visited outpatient clinics, as *moderately affected*; subjects who responded, as having symptoms but who did not seek medical attention as *slightly affected*.

Subjective symptoms at acute phases are shown in Fig. 1. Miosis-related ocular symptoms such as darkness or narrowing of visual fields, blurred vision, and ocular pain were frequently observed. Headache, dyspnea, cough and rhinorrhea were also common. In moderately affected subjects, rhinorrhea was frequent, followed by darkness of visual field, dyspnea and headache. In slightly affected subjects, rhinorrhea was most frequent. Headache, dyspnea, cough and ocular pain were observed in 20% or less. Rhinorrhea disappeared quickly. Subsequently cough, dyspnea and nausea disappeared.

Three weeks later, 28% of the affected subjects remained symptomatic: 69.4% of those severely affected; 42%, of those moderately affected; and 13.9%, of those slightly affected. The most frequent persisting symptoms were fatigue, dysesthesia of extremities and ocular pain. Dark vision, narrowing of visual field, blurred vision and dizziness continued in about 10% of severely affected subjects. Symptoms that remained in moderately affected subjects were dark vision, ocular pain and dysesthesia of extremities [33].

Miosis and related ocular symptoms were the most frequent toxic manifestations. Miosis was the most common sign. In 219 subjects, diameter of pupils and serum cholinesterase were measured in the acute phase (Fig. 2). In subjects who showed marked miosis (below 1.0 mm pupil

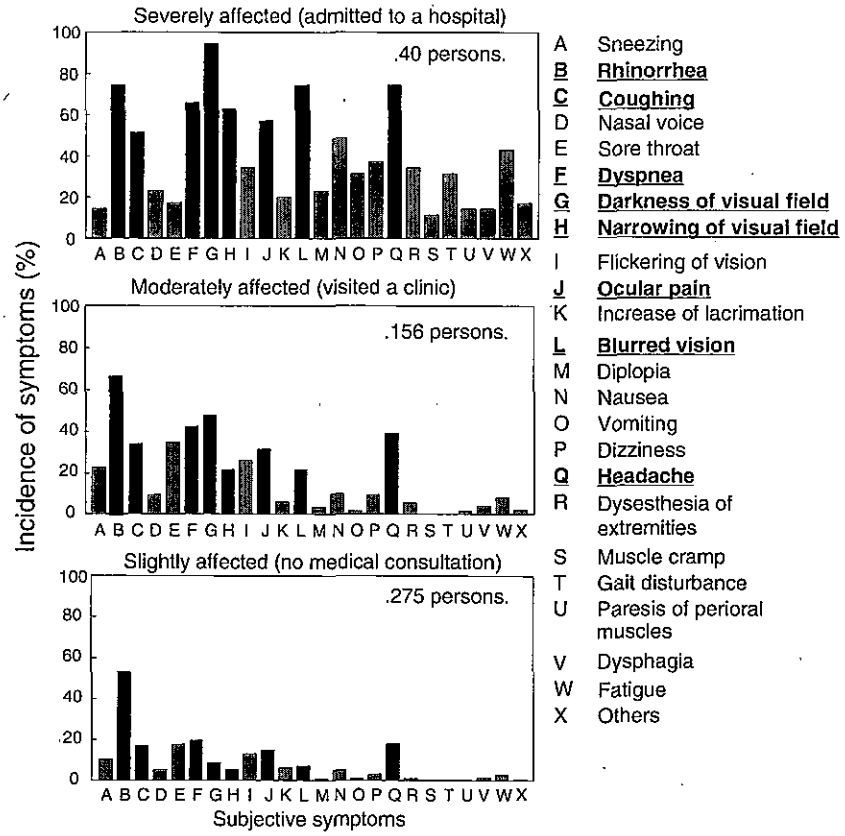

Fig. 1. Subjective symptoms at acute phases in 471 residents in Matsumoto Sarin incident. Data were obtained from a survey conducted at 3 weeks after the incident. From Ref. [33].

diameter in 21 cases) and moderate miosis (1.0–2.0 mm pupil diameter in 93 cases), serum cholinesterase activity ranged widely from below 10% to above 200% of the lowest normal value. The data suggested that both systemic and topical contact with Sarin caused marked to moderate miosis, whereas patients without miosis (above 3.0 mm pupil diameter) could be considered unaffected because no decrease of serum cholinesterase activity was observed in them. Miosis uniformly disappeared with 1 month [23,33].

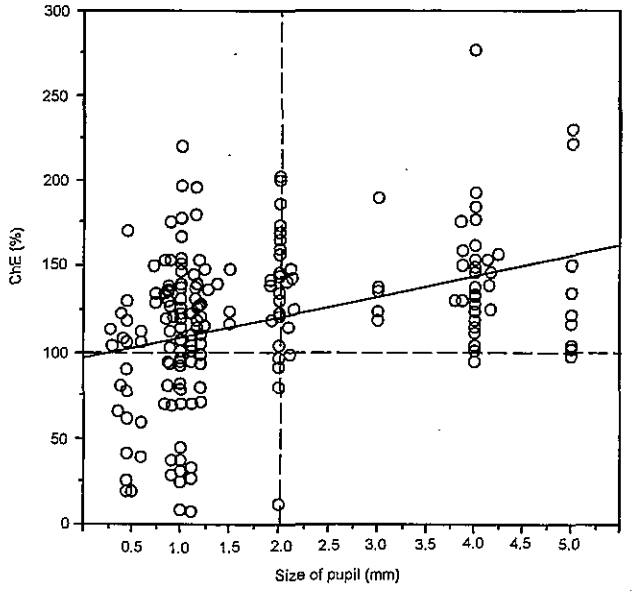

Fig. 2. Relationship between size of pupil and serum Cholinesterase activity in Matsumoto incident.

Salivation, rhinorrhea, diarrhea commonly occurred in severely affected subjects. Nicotinic symptoms such as muscular twitch and weakness were infrequent and were noted only in critically to severely affected people. Bradycardia was infrequent; however, tachycardia was common in critically affected subjects during the first few hours, indicating that nicotinic symptom was dominant.

Loss of consciousness and generalized convulsion occurred in critically injured subjects but disappeared within a week without sequelae. Dementia was not observed in any victims after recovery from consciousness disturbance or convulsion [15,33]. Severely affected subjects showed muscular hypotonia, weakness and areflexia, which disappeared within a week. Dysesthesia of distal parts of extremities were observed in 16 subjects treated for acute intoxication, disappearing within 1 month in most cases. A decrease in Achilles tendon reflex and vibration sense in the distal legs correlated with miosis.

Serum cholinesterase (ChE) was examined in 105 subjects who were admitted to hospitals or visited a hospital

within 2 days of the incident. Forty-five (42.9%) showed a decrease. Erythrocyte acetylcholinesterase (E-AchE) was measured in 18 admitted to hospitals initially and in 58 outpatients, seen within 3 weeks. Twenty showed decreases. It returned to normal within 3 months. Serum creatine kinase (CK) was elevated in 33 subjects of 155 examined. Severely affected subjects showed significant elevation compared to slightly affected or unaffected subjects.

Leukocytosis was observed in severely affected subjects (10,972±4074; mean±SD in 18 subjects) ($p<0.0001$). Erythrocytes counts were normal. Serum potassium and chloride decreased significantly in severely affected subjects with values that correlated with ChE ($p<0.0001$ for K, and $p=0.0019$ for Cl). Hyperglycemia, ketonuria and low serum triglyoride, which are attributes to Sarin effects on the adrenal medulla, were observed in the most severely affected subjects. EKG abnormalities were observed in 5 out of 39 subjects examined, i.e., supraventricular or ventricular extra systole, A–V conduction block or atrial fibrillation. ChE was 40.7% of the lowest normal value for the group with abnormal EKG, whereas it was 72.0% for the EKG normal group. EEGs in 9 severely affected subjects and in 2 who developed convulsions, all showed epileptiform discharges.

Eighteen teams consisting of 52 people from 5 fire departments engaged in rescue activities. Although a gas poisoning was suspected initially, the health care workers were not protected from contamination. Of the 52, 8 suffered subjective symptoms. Ocular symptoms, including pain and dark vision, headache, nausea, and rhinorrhea were noted. Although most did not consult with doctors, one with severe intoxication was admitted to a hospital [19,27].

He engaged in rescue activities near the Sarin emission site for 5 h, complained of headache and nausea and was admitted to a hospital. Pinpoint pupils and conjunctival injection were present. Laboratory examination indicated glycosuria and ALT of 49 IU. After O_2 inhalation treatment and atropine sulphate injection, he was normal by the next day.

2.2. Treatment and follow up

Atropine sulphate, benzodiazepines, and intravenous fluid infusions were effective for muscarinic symptoms, epileptic convulsion, agitation and body fluid loss. Severely affected subjects required intubations and mechanical ventilation [33].

Organophosphate poisoning was suspected in patients seen in the six hospitals. Despite quick recovery of other problems, muscarinic symptoms and especially miosis were resistant to atropine sulphate. Some patients were treated with multiple doses of tens of milligrams of atropine sulphate intermittently during a 24-h period.

All residents in the affected areas were subject to health checks and questionnaire surveys at 3 weeks, 3 months, 1 year, 2 years 8 months, and 10 years after the incident. All affected individuals were provided with medical care whenever they sought attention.

The 3-week responses were collected from 1,743 residents and a retrospective study of subjective symptoms during the acute phase was made. (Fig. 1)

Of 155 subjects who received medical evaluation; 76 requested physician's attention. Symptoms included dysesthesia of extremities (16 subjects), rhinorrhea (14), ocular pain (14), darkened vision (13), and easy fatigability (12). On physical examination, only one subject showed miosis. Otherwise, there were no neurological or physical signs correlated to Sarin poisoning. On laboratory examination, 13 showed low EAchE activity.

At the 3-month assessment, no one demonstrated physical findings or laboratory abnormalities.

Table 1
Subjective symptoms at 1 year and 2 years 8 months surveys (Matsumoto)

	One year survey					Two years 8 months survey	
	Severe 11 (100%)	Moderate 26 (100%)	Slight 17 (100%)	Total* *n* (%)	Relation to E-AchE decrease at acute phase**	All victims 167 (100%)	Odds ratio (95% CI)***
Asthenopia	11 (100)	16 (61.5)	11 (64.7)	38 (70.4) ns	$p<0.05$	40 (24.0)	9.72 (5.54–17.04)
Fatigue	11 (100)	17 (65.4)	7 (41.3)	35 (64.8) $p<0.001$	$p<0.001$	25 (15.0)	5.18 (2.84–9.44)
Blurred vision	7 (63.6)	12 (46.2)	11 (64.7)	30 (55.6) ns	ns	18 (10.8)	6.10 (2.92–12.72)
Asthenia	9 (81.8)	5 (19.2)	4 (23.5)	18 (33.3) $p<0.05$	$p<0.01$	14 (8.4)	5.47 (2.44–12.29)
Palpitation	3 (27.3)	3 (11.5)	0 (0)	6 (11.1) $p<0.05$	ns	5 (3.0)	4.10 (1.17–14.33)
Nightmare	3 (27.3)	3 (11.5)	0 (0)	6 (11.1) ns	ns	5 (3.0)	2.92 (0.92–9.32)

Severe: admitted to a hospital at the acute phase.
Moderate: visited a clinic at the acute phase.
Slight: had symptoms but did not consult with a doctor.
Total*: the total number of subjects complained symptoms. *Significance in difference in frequencies of having symptoms between affected and unaffected subjects at the acute phase.
**Significance of decrease in erythrocyte acetyl-cholinesterase activity (E-AchE) at the acute phase in subjects who had symptoms at 1 year survey.
***Odds ratio of having symptoms at the 2 years 8 months survey between victims and non-victims at the acute phase.
From Ref. [17].

At 1-year assessment, responses were obtained from 1,238 subjects (60.3%). Of these, 318 subjects had subjective symptoms and 919 did not. Results were described elsewhere [17].

Of the 318 victims, 58 had subjective symptoms which could be related to Sarin. Of these, 11 had been severely affected, 26 were moderately affected and 17 were slightly affected during the acute phase. The frequency of some symptoms in each group is listed in Table 1. The E-AchE level during the acute phase among those who did or did not have each symptom is also listed. Asthenopia, fatigue and asthenia were prominent, more frequent in those who were more severely affected in the acute phase. Blurred vision, shoulder stiffness, insomnia, palpitation were noted infrequently.

One hundred forty six victims with pupil diameter <2 mm and 53 with a serum ChE level <100% (the lower limit of normal) at the acute phase were invited to have a medical evaluation after 1 year. Of the 154, 72 (46.8%) responded. Sensory polyneuropathy, abnormal and premature ventricular contraction in critically affected subjects persisted (Table 2). One subject fulfilled criteria for the clinical characteristics of post-traumatic stress disorder (PTSD) [30].

Those who had been severely affected initially and all those who did have the one-year evaluation were evaluated at 18 months. Six subjects who showed abnormalities in EEG, ECG, nerve conduction study at the 1 year study, showed persisting abnormalities without clinical signs. A subject in a vegetative state was unchanged. One person, who had suffered severely with moderate disturbance of consciousness, showed an EEG with 14 Hz positive spikes. She was asymptomatic and normal on examination. The EEG findings disappeared within 3 years. EEG abnormalities disappeared in all 4 asymptomatic subjects within 5 years. Other abnormalities, one each per subject were peripheral nerve lesions, ECG abnormality (PVC), hypoxemia, low grade fever.

Only one subject suffered severely at the incident with 12% ChE activity, showed slightly low responses in electroretinogram (ERG) after 5 years [22]. Sensory neuropathy with peripheral dysesthesia, PVC, and low grade fever persisted in one person each [14].

Psychiatrists, psychoanalysts and an epidemiologist conducted interviews and psychological tests at 5 years. EEG and autonomic nervous function tests were performed. Partial PTSD was suspected in 6 subjects. Of those, one had been severely injured acutely and one moderately, while four had been slightly injured. Symptoms were flashbacks and exaggerated reactions elicited by looking at scenes remembering of the poisoning incident. Characterological and environmental factors were considered to be contributing factors for PTSD in all 6. EEG and autonomic nervous function tests were normal [14].

Although the incidence of PTSD was low, psychological complaints persisted in a considerable number of people who had been in the area of the Sarin event whether or not physical findings had been demonstrated acutely [14].

The last systematic questionnaire survey was conducted 9 years, 6 months after the incident (Nakajima et al., unpublished data). Subjects (1813) studied were those living in the area (1776), those severely affected acutely and who had moved to other places (24) and staffs of rescue teams (13). Six hundred sixty-eight consented to the survey. The questionnaire consisted of subjective symptoms similar to the previous surveys (33 items), those related to psychological problems (22 items) and affection with physical or neuropsychiatric diseases after the incident (20 diseases).

Symptoms which showed high odds ratio between affected and unaffected citizens were asthenopia and psychic symptoms including flashback, nervousness and loss of concentration.

Common diseases frequently noted in the affected victims included cardiac diseases (odds ratio 11.52), eye diseases (4.50) and ear or nose diseases (7.27).

The patient with anoxic encephalopathy was unchanged. Arrhythmia (PVC) in one person persisted on without other signs of cardiac dysfunction.

Table 2
Summary of health check at 1 year (Matsumoto)

Subject no.	Ch E (%)* at acute phase	Findings at 1 year
1	7	Hypoxemia (SaO_2 65–74%)
2	8	Anoxic encephalopathy
3	12	Low grade fever
4	12	EEG: delta wave, Sensory neuropathy
5	19	EEG: sharp wave, Premature ventricular contraction (PVC)
6	21	EEG: paroxysmal discharge in sleep
7	24	Tachycardia with Holter ECG
8	33	Normal
9	39	Normal
10	39	Normal
11	41	Normal
12	59	Normal
13	66	Lowering sensitivity to visual field test
14	69	Normal
15	77	Normal
16	82	Normal
17	90	Concentric constriction of visual field Admission with ulcerative colitis suffering prior to the incident.
18	91	Normal
19	93	Normal
20	96	Normal

*Serum cholinesterase activity. 100% is the lowest normal value in each institution. From Ref. [30].

3. The Tokyo subway incident

At about 8:00 AM on Monday, March 20th, 1995, Sarin became airborne after terrorists broke plastic bags containing

fluid with 30% Sarin in fully peopled subway cars, all headed to the center of governmental offices. Twelve people died: six within 2 h of exposure and six from 20 to 80 days later. Sarin and its metabolites were detected in many specimens.

Treatment outcomes have also been reported elsewhere [13,24,25,28,29].

These data and a questionnaire survey to all victims are summarized in this article.

3.1. Clinical observations

Six hundred forty victims of Sarin poisoning arrived at St. Luke's Hospital within hours of the incident. They were categorized into three groups: A, 5 critically or severely injured people exhibited CPA or required mechanical ventilation; B, 107 (16.7%) moderately injured people were characterized by systemic symptoms and signs of respiratory, digestive and/or neurological (central, peripheral or autonomic) systems in addition to ocular signs; C, mildly affected subject (528 or 82.5%) were those who had only eye signs or symptoms and were released after several hours' observations.

Of 5 critically injured subjects, 3 arrived at the hospital in CPA. One exhibited mioses and was unresponsive to resuscitation and died. A second was resuscitated but suffered severe anoxic brain damage and died 28 days later. The serum ChE was 6% of the lowest normal value. A 3rd person remained in deep coma after spontaneous recovery of heart beat, demonstrating generalized convulsions controlled by intravenous diazepam. Pralidoxime iodide (PAM) was effective and respiratory distress and miosis recovered quickly with serum ChE level [25]. The other two had generalized convulsions, consciousness disturbance and respiratory failure. After diazepam and mechanical ventilation, both recovered quickly and were discharged three and 5 days later. Consciousness disturbances (19 cases, 17.1%) and convulsions (3 cases, 2.7%) were observed in severely or moderately injured subjects [29].

Signs and symptoms of 107 moderately injured subjects and 4 severely injured subjects are shown in Table 3 [25]. In addition to miosis and related ocular symptoms (eye pain, blurred vision, visual darkness), gastrointestinal (nausea, vomiting), respiratory (dyspnea, cough) and neuropsychiatric (headache, fasciculation, agitations) symptoms and signs were observed. These are similar to the symptoms experienced in Matsumoto incident in content and frequencies. In some victims numbness of extremities (18.9%) and vertigo or dizziness (8.1%) were recorded [29].

Of 85 victims treated in the Keio University Hospital, 1 was dead on arrival and 15 were admitted. All others were treated at an outpatient clinic [24].

Serum cholinesterase (ChE) and erythrocyte acetyl cholinesterase (AchE) levels were measured in all subjects before treatment with atropine sulphate or oximes. Correlation was made between AchE and pupil size before treatment on the day of the incident. In subjects with miosis (pupil size below 3 mm), 32 showed decrease of AchE (below 1.2 U, the lowest of normal) and 18 were normal. In subjects with marked miosis (1.0 mm or below), 74% showed decrease in AchE.

Table 3
Signs and symptoms of 111 subjects admitted to St. Luke's Hospital

Signs or symptoms	Subjects (%)
Miosis	99.0
Headache	74.8
Dyspnea	63.1
Nausea	60.4
Eye pain	45.0
Blurred vision	39.6
Visual darkness	37.8
Vomiting	36.9
Easy fatigability	36.9
Cough	34.2
Agitation	33.3
Fasciculation	23.4
Convulsion	2.7

From Ref. [25].

Although there is not data specific to rescue team staffs, they worked without special protections against contamination. The Tokyo Teishin Hospital received 71 casualties including 39 rescue team members. Of the 71, 43 including 25 rescue staffs were admitted to the hospital for treatment. Of the 71, 41 showed miosis. Dark vision, headache, nausea, discomfort, cough, tightness of the chest were common symptoms. Locomotor ataxia, which disappeared in 2 days, was observed in 3 subjects. None of the 71 had alterations of consciousness or seizures [13].

In St. Luke's Hospital, of 472 health care personnel working with poisoned people, 110 (23%) complained of Sarin poisoning symptoms; eye symptoms (66), headache (52), throat pain (39), dyspnea (25), nausea (14) or dizziness (12) [28].

3.2. Treatment and follow up

Two hours after the Tokyo Subway incident, Sarin was identified as the causative agent. Critically injured subjects either died or recovered. Those who did not die or suffer irreversible anoxic encephalopathy, recovered quickly to normal. Pralidoxime iodide (PAM) and 2-pyridine aldoxime methiodide (2-PAM) were administered intravenously from 2 to 6 h after the Sarin exposure. Erythrocytes AchE level recovered to normal in 13 to 72 days [29]. Blood purification was reported effective [35].

Six months after the incident, 150 victims, of those conveyed to the St. Luke's Hospital at the incident, were invited to undergo a neurological evaluation. Eighteen people consented [16,34]. None had neurological signs

attributable to Sarin poisoning. In neurophysiological tests, prolongation of latencies of event-related potentials P 300, thought to reflect cognitive process in the brain, and late component P 100 of visual evoked potentials (VEP) occurred in affected subjects with group comparison. Brainstem auditory evoked potentials (BAEP) were normal [16]. Postural stability test using a force-plate showed larger postural sway of low frequency (below 1 Hz) in female victims, suggesting long-lasting effects on the vestibulocerebellar system [34].

As an indicator of peripheral autonomic nerve functions, the coefficient of variations of RR intervals in ECG (CV_{RR}) was reduced significantly in affected subjects as a group and the value in each subject correlated to the reduction of ChE at the acute phase [16].

PTSD scores were significantly higher in Sarin victims than in matched control subjects ($p<0.05$). In particular, scores on items regarding disturbing memories, feeling incident happening, physical reactions to remembering, avoid thinking or situations reminding Tokyo Sarin incident, were higher in the victims [16].

A survey conducted 6 months later consisted of a general health questionnaire (GHQ), a self-rating depression scale (SDS) and 23 questions on symptoms related to PTSD. The questionnaires of 408 (36.9%) were judged appropriate for analysis. Thirty-two (7.8%) fulfilled the DSM-IV criteria of PTSD [10].

Another study of 56 rescue workers was made 3 years later. Neurobehavioral tests included variations in gravity shift on standing, vibration sense, finger-tap speed, simple and choice reaction times, digit span and Benton visual retention test. Of these tests, only backward digit span was lowered in Sarin victims in a dose-effect manner ($p=0.07$) [21]. Otherwise, the studies did not indicate any clinical sequelae in Sarin poisoning victims.

Of 34 Sarin poisoning victims admitted to the St. Luke's Hospital, 11 (32.4%) were diagnosed with PTSD by standard tests 5 years later [26].

Another questionnaire survey was sent to 1350 victims at 5 years with 655 respondents. Common symptoms were asthenopia (60.9%), blurred vision (43.8%), easy fatigability (37.1%), difficulty in concentration (35.6%), difficulty in near vision (32.7%), and headache (32.2%).

Of 5311, who reported to police offices contact with Sarin at the incident, 1247 responded to a questionnaire at 3 years [20]. More than half complained of physical symptoms such as asthenopia (51.1% immediately after the incident, 33.5% 3 years after) and decrease in visual acuity (38.0% immediately after, 28.3% 3 years after) and psychological trauma including vivid memories of the incident (33.0% immediately after, 17.5% 3 years after), inability to ride on subways (30.1% immediately after, 13.9% 3 years after).

A national health insurance covered Sarin casualties including PTSD in the Tokyo incident. Three thousand seven hundred and one including 11 dead received some compensation. Of these, 23 were still receiving compensation (as of 2/28/05), with 35 under continuing care because of worsening problems.

4. Discussion

Because of these 2 incidents, a variety of medical data was gathered on acute and chronic effects of Sarin in humans. Its pathophysiology is discussed elsewhere in this publication.

Inhalation of Sarin gas can cause immediate death. In the Matsumoto incident, 4 dead victims were found in rooms where they lived, even though Sarin gas was expelled in the open air 40 to 60 meters away. Some showed signs of having had generalized convulsions. The primary cause of death was probably respiratory arrest. In the Tokyo incident no such deaths occurred.

In both events, several victims with CPA were taken to hospitals. The courses of illness varied in each. Some victims died, unresponsive to resuscitation efforts. One who was resuscitated had severe anoxic encephalopathy and died; another remains in a vegetative state. Several young subjects who were resuscitated left the hospital within several days without any apparent sequelae. These subjects had suffered from generalized convulsion after recovery of spontaneous heart beats. Consciousness recovered gradually within several hours after atropine sulphate, oximes, diazepam, intravenous fluid infusion and respiratory support [15,25,33].

The main site of Sarin action in critically ill victims was on the central nervous system; including convulsions and coma. A rapid, complete recovery from critically ill state is a unique characteristic of Sarin poisoning compared to organic phosphate insecticides which may cause overt chromic neuropsychiatric sequelae including amnesia, confusion, ataxia and polyneuropathy.

Sarin inhibits AchE activity in the central, peripheral and autonomic nervous systems. Signs and symptoms due to hyperactivity of Ach on these systems were observed in both of the two incidents [15,29]. Nicotinic effects on the neuromuscular transmission were observed in severely affected subjects; including muscular weakness and hypotonia, loss of deep tendon reflex and twitch or fasciculation of muscles.

Neuropathy with dysthesia and decrease in vibration sense was observed in severely affected subjects. Although clinical signs disappeared mostly within several weeks, they lasted more than 5 years in one person in the Matsumoto incident. Transient locomotor ataxia was reported after the Tokyo incident [13]. Ataxia has been observed in experimental animals as a delayed effect of Sarin [7].

Muscarinic signs were most prominent in severely to slightly affected victims. Among them, miosis and related symptoms such as dark vision, blurred vision and ocular pain were most frequently observed in subjects who came to

hospitals (Fig. 1) [11,29,33]. In slightly affected subjects in the Matsumoto incident, rhinorrhea was the most frequent symptom (more than 50%) followed by dyspnea, cough and headache observed in about 20% of subjects.

Effects of Sarin on the heart were either tachycardia as a nicotinic effect observed in severe cases, or bradycardia as a muscarinic effect observed in moderate cases.

Abnormal laboratory findings attributable to Sarin effects on the adrenal medulla were noted [15].

High CK level in severely affected subjects were secondary to a direct action with Sarin on skeletal muscles [1,6,8,15,25].

Pralidoxime iodide does not pass through the blood–brain barrier; however, its administration reversed serum ChE levels and miosis quickly if administered within 6 h of Sarin inhalation [25]. A correlation between pupil size and the serum ChE level were examined in both incidents. Subjects with miosis (pupil's diameter <2.0 mm) showed a wide range of ChE level from very low to normal (Fig. 2). Miosis is caused by either inhalation or topical absorption by the cornea or conjunctive. In the latter cases, only eye symptoms may exist. Subjects recovered without any specific treatment in the Matsumoto incident. The same relation between pupil size and ChE or erythrocyte AchE level was observed in the Tokyo subway incident [11,24]; however, there were a few cases with normal pupil size and low AchE level [24].

Serum ChE is not an exact indicator of acetylcholinesterase level; however, it is more easily measured than is erythrocyte AchE activity. In both Japanese Sarin events, serum ChE proved to be an effective measure for loss of acetylcholinesterase functions. In those critically and severely affected by Sarin, convulsions and EEG abnormalities occurred. Epileptic convulsions were controlled within a few hours, but EEG abnormalities without seizures lasted for years in 4 severely affected victims in the Matsumoto incident, disappearing within 5 years. EEG changes have been reported as long-term effects after Sarin poisoning in animals and humans [2,4]. Long-lasting brain dysfunctions were studied in victims of the Tokyo subway incident. Abnormalities in an event-related potential P300, visual evoked potentials [16] and in digit span test [21] were noted 6 month and/or 3 years after the incident. Animal studies document nerve cell degeneration in the hippocampus and thalamus [9].

Although the long-term effects of Sarin on cognitive functions are matter of great concern, no subjects demonstrated dementia on medical checks up to 10 years later. Long-term subjective symptoms are listed in Table 4. Forgetfulness, chronic lack of concentration and depressive mood were observed more in exposed than not exposed subjects in the Matsumoto incident.

In the Matsumoto incident, signs of peripheral nerve dysfunction including dysesthesia, decrease in vibration sense and loss of the deep tendon reflexes were observed in the acute phase in severely affected victims. These signs disappeared quickly; however, a delay in the nerve conduction time persisted in one subject at the 5 year evaluation. Delayed neuropathy after organophosphorous compounds is reported after Sarin exposure in experiment animals [3,5]. Delayed effects on the autonomic nervous system were not noted in either of the incidents. One subject showed chronic PVC's after the Matsumoto incident. Sarin intoxication caused cardiomyopathy in animal studies [31].

Table 4
Subjective symptoms which may have a relation to cognitive dysfunctions

Symptoms	St. Luke's Hospital patients (*n*)		NPO Tokyo (*n*)	Matsumoto 5 years (*n*)	
	2 years (283)	5 years (191)	5 years (655)	Pts (88)	Cont. (87)
Forgetfulness	11.7%	12.6%	24.3%	19.5%	12.6%
Diminished interest and apathy	6.4	5.8	11.5	3.4	3.4
Lack of concentration	7.8	8.4	19.8	16.0	4.6
Depressive mood	14.8	13.3	24.1	17.1	6.8

From questionnaire surveys with 14 items for physical, 8 for eye and 11 for psychic symptoms (Ishimatsu's form). Items listed above are from psychic symptom questions. Adopted from data by Kawana et al. [12] and Matsumoto Regional Comprehensive Medical Council [14].

In Tokyo the coefficient of variation of RR intervals in ECG (CV_{RR}) was measured at 6 months. Reduction of CV_{RR}, which is a sign of loss of parasympathetic innervation to the heart, was observed with a positive correlation with reduction of ChE at the acute phase [16].

Because a main concern was to prevent psychological sequelae, repeated questionnaire surveys, health checks, town meetings were done for 10 years in Matsumoto. Psychological problems were not apparent in health checks. Only 6 people were diagnosed with PTSD by psychiatrists at the 5 year medical evaluation. However, in the Matsumoto event, 73% of exposed people and 44% of those not exposed reported psychological problems in a questionnaire survey after 10 years ($p<0.001$). A similar situation occurred after the Tokyo incident [26]. A majority of people exposed after both incidents are now in good physical health. However, acute and long-lasting psychological problems and PTSD were common. These psychological problems affected quality of life and are important socio-medical issues.

5. Future issues and the role of neurologists

Giving the experiences of Sarin incidents in Japan, the following are considered important for preparedness in future.

1. Establishment of treatment.
2. Long-term health checks and follow-up of psychic problems.

Despite low frequency of neurological sequelae, they may last up to 5 years. A team of neurologists, psychiatrists and epidemiologists should be a core of follow up systems. Collaboration with administration and health care personnel is important.

Neurological and medical health checks are of limited value in a mobile community. However, questionnaire surveys should be developed.

3. The role of neurologists in terrorist attacks which use nerve agents is as part of a rescue team.

A rapid diagnosis of the causative agent and serum ChE measurement is essential. Although miosis is a clue with high sensitivity and specificity, it is not an indication of severity and cannot be used for triage of victims. In long-term follow-up, neurologists should work in close collaboration with psychiatrists and epidemiologists. Education of affected and non-affected victims should be done.

Acknowledgement

We thank Dr. Leon Prockop (University of South Florida) for editing the manuscript.

References

[1] Bright JE, Inns RH, Tuckwell NJ, Griffiths GD, Marrs TC. A histochemical study of changes observed in the mouse diaphragm after organophosphate poisoning. Hum Exp Toxicol 1991;10:9–14.
[2] Burchfiel JL, Duffy FH. Organophosphate neurotoxicity: chronic effects of Sarin on the electroencephalogram of monkey and man. Neurobehav Toxicol Teratol 1982;4:768–78.
[3] Crowell JA, Parker RM, Bucci TJ, Dacre JC. Neuropathy target esterase in hens after Sarin and soman. J Biochem Toxicol 1989;4:15–20.
[4] Duffy FH, Burchfiel JL, Bartels PH, Gaon M, van Sim M. Long-term effects of an organophosphate upon the human electroencephalogram. Toxicol Appl Pharmacol 1979;47:161–76.
[5] Goldstein BD, Fincher DR, Searle JR. Electrophysiological changes in the primary sensory neuron following subchronic soman and Sarin: iterations in sensory receptor function. Toxicol Appl Pharmacol 1987;91:55–64.
[6] Gupta RC, Dettbarn WD. Potential of memantine, D-tubocurarine, and atropine in preventing acute myopathy induced by organophosphate nerve agents: soman, Sarin, tabun and VX. Neurotoxicology 1992;13:649–61.
[7] Husain K, Vijayaraghavan R, Pant SC, Raza SK, Pandy KS. Delayed neurotoxic effect of Sarin in mice after repeated inhalation exposure. J Appl Toxicol 1993;13:143–5.
[8] Inns RH, Tuckwell NJ, Bright JE, Marrs TC. Histochemical demonstration of calcium accumulation in muscle fibers after experimental organophosphate poisoning. Hum Exp Toxicol 1990;9:245–50.
[9] Kadar T, Shapira S, Cohen G, Sahar R, Alkalay D, Raven L. Sarin-induced neuropathology in rats. Hum Exp Toxicol 1995;14:252–9.
[10] Kadokura M, Ushijima S, Ogawa Y, Shimizu H, Agata T, Yamamura T. Post traumatic stress disorder in victims of an attack with Sarin nerve gas on the Tokyo subway system. Rinsho Seishin Igaku 2000;29:677–83.
[11] Kato T, Hamanaka T. Ocular signs and symptoms caused by exposure to Sarin gas. Am J Ophthalmol 1996;121:209–10.
[12] Kawana N, Ishimatsu S, Kanda K. Victims of the terrorist Sarin attack on the Tokyo subway system. Rinsho Seishin Igaku, Special Issue 2002:139–45.
[13] Masuda N, Okuda T, Miyazaki S, Takatsu M, Ito K, Kanetaka T, et al. Clinical and laboratory data in 71 patients with Sarin poisoning. Teishin Igaku 1995;47:387–90.
[14] Matsumoto Regional Comprehensive Medical Council. Health emergency control system in Matsumoto city. Health Hyg Matsumoto 2000;22:1–107 [supplement].
[15] Morita H, Yanagisawa N, Nakajima T, Shimizu M, Hirabayashi H, Okudera H, et al. Sarin poisoning of citizens in Matsumoto. Lancet 1995;346:290–3.
[16] Murata K, Araki S, Yokoyama K, Okumura T, Ishimatsu S, Takasu N, et al. Asymptomatic sequelae to acute Sarin poisoning in the central and autonomic nervous system 6 months after the Tokyo subway attack. J Neurol 1997;244:601–6.
[17] Nakajima T, Ohta S, Fukushima T, Yanagisawa N. Sequelae of Sarin toxicity at one and three years after exposure in Matsumoto, Japan. J Epidemiol 1999;9:337–43.
[18] Nakajima T, Ohta S, Morita H, Midorikawa Y, Mimura S, Yanagisawa N. Epidemiological study of Sarin poisoning occurred in Matsumoto City, Japan. J Epidemiol 1998;8:33–41.
[19] Nakajima T, Sato S, Morita H, Yanagisawa N. Sarin poisoning of a rescue team in the Matsumoto Sarin incident in Japan. Occup Environ Med 1997;54:697–701.
[20] National Police Academy, Police Science Institute. A report on casualties of the subway Sarin incident. Keisatsu Koron (Police Public Opinion) 1999;54:37–47.
[21] Nishiwaki T, Maekawa K, Ogawa Y, Asukai N, Minami M, Omae K, Sarin Health Effects Study Group. Effects of Sarin on the nervous system in rescue team staff members and police officers 3 years after the Tokyo subway Sarin attack. Environ Health Perspect 2001;109: 1169–1173.
[22] Nohara M. Opthalmological health checks after Sarin exposure. In: Matsumoto Regional Comprehensive Medical Council, editor. Health Hyg Matsumoto, vol. 22; 2000. p. 42–51. Suppl.
[23] Nohara M, Segawa K. Ocular symptoms due to organophorus gas (Sarin) poisoning in Matsumoto. Br J Ophthalmol 1996;80:1023.
[24] Nozaki H, Hori S, Shinozawa T, Fujishima S, Takuma K, Kimura H, et al. Relationship between pupil size and acetylcholinesterase activity in patients exposed to Sarin vapour. Intensive Care Med 1997;23: 1005–1007.
[25] Ohbu S, Yamashita A, Takasu N, Yamaguchi T, Murai T, Nakana K, et al. Sarin poisoning on Tokyo subway. South Med J 1997;90: 587–93.
[26] Ohtani T, Iwanami A, Kasai K, Yamasue H, Kato T, Sakaki T, et al. Post traumatic stress disorder symptoms in victims of Tokyo subway attack: a 5 years follow-up study. Psychiatry Clin Neurosci 2004;58:624–9.
[27] Okudera H, Morita H, Iwashita T, Shibata T, Otagiri T, Kobayashi S, et al. Unexpected nerve gas exposure in the city of Matsumoto: report of rescue activity in the firs Sarin gas terrorism. Am J Emerg Med 1997;15:527–8.
[28] Okumura T, Suzuki K, Fukuda A, Koyama, Takasu N, Ishimatsu S, et al. The Tokyo subway Sarin attack: disaster management: Part 1. Community emergency response: Part 2. Hospital response: Part 3. National and international responses. Acad Emerg Med 1998;5: 613–628.
[29] Okumura T, Takasu N, Ishimatsu S, Miyanoki S, Mitsuhashi A, Kumada K, et al. Report on 640 victims of the Tokyo subway Sarin attack. Ann Emerg Med 1996;28:129–35.
[30] Sekijima Y, Morita H, Yanagisawa N. Two-year follow-up study of victims of Sarin poisoning in Matsumoto, Japan. Ann Intern Med 1997;127:1042.
[31] Singer AW, Jaax NK, Graham JS, McLeod Jr CG. Cardiomyopathy in soman and Sarin intoxicated rats. Toxicol Lett 1987;36: 243–9.

[32] Suzuki J, Kohno T, Tsukagoshi M, Furihata T, Yamazaki K. Eighteen cases exposed to Sarin in Matsumoto, Japan. Int Med 1997;36:466–70.
[33] Yanagisawa N, editor. Report for Toxic Gas Attack in Matsumoto. Matsumoto Regional Comprehensive Medical Council; 1995.
[34] Yokoyama K, Araki S, Murata K, Nishitani M, Okumura T, Ishimatsu S, et al. A preliminary study on delayed vestibulo-cerebellar effects of Tokyo subway Sarin poisoning in relation to gender difference: frequency analysis of postural sway. J Occup Environ Med 1998;40:17–21.
[35] Yokoyama K, Ogura T, Kishimoto M, Hinoshita F, Hara S, Yamada A, et al. Blood purification for severe Sarin poisoning after the Tokyo subway attack. JAMA 1995;274:379.