Case report

Case report: Long-term cognitive sequelae of sarin exposure

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ABSTRACT

The long-term sequelae of acute sarin exposure are not well understood. The largest clinical cohort resulted from the 1994 and 1995 attacks in Japan. Observers noted mostly psychiatric sequelae, with a high prevalence of post-traumatic stress disorder (PTSD). We describe neurocognitive findings that may represent sequelae of low-level sarin exposure in Iraq.

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1. Introduction

Nerve agent exposure has garnered public attention in the recent decade. Sarin, an organophosphate acetylcholinesterase inhibitor, first became a household term after the Tokyo subway bombing by Aum Shinriyko in 1995. Since then, the world has seen a rash of chemical and biological terrorist activity to include the anthrax release into the US postal system. A result is the increasing awareness of the potential for smaller organizations to turn to chemical and biological agents as their weapon of choice. These are cheap, can be delivered in mass quantities and may have the added psychological impact of contagious or delayed effects.

The US invasion of Iraq was driven partly by the fear of such effects and consequently the decision to deter a suspected nuclear, biological, and chemical threat. Although US forces never found production or storage facilities, the first cases of exposure with weaponized sarin emerged in the summer of 2004. The insurgency made public news with these first chemical casualties when two soldiers were exposed to sarin gas by means of an improvised explosive device (IED).

The long-term neurologic sequelae of sarin exposure remain unclear. What little literature exists comes almost entirely from the Japanese healthcare system's experience with the casualties and healthcare workers of the Tokyo subway bombing. The majority of this body of literature encompasses only the psychiatric sequelae, given the high prevalence of post-traumatic stress disorder. We describe the neurocognitive sequelae of one of the two incipient cases of exposure in Iraq, which is, to our knowledge, the first description of sarin exposure since 1995 and the first ever report of a sarin combat casualty.

2. Case report

A 34-year-old right-handed Caucasian male senior Army explosive ordnance disposal (EOD) sergeant was exposed to sarin in May of 2004 while deployed to Iraq. The patient was called to disarm an IED after a blast was reported. Upon arrival, he and his assistant picked up the IED and rapidly loaded it in their enclosed vehicle in an effort to evacuate the area, which was still under enemy fire. Several minutes later, while driving towards their headquarters, the patient and his assistant had the onset of confusion, dyspnea, blurred vision, and severe headache. Upon arrival to their headquarters, they were immediately given oxygen and observed. Initial serologies and chemistries were drawn normal. In the meantime, the IED was inspected and $3–5\ cm^3$ of a colorless liquid was discovered inside the vehicle, which was later identified as sarin. The patient demonstrated erythrocyte cholinesterase (RBC-ChE) activity of 2.88 U/ml (0.46 delta pH unit/h), which represented a 39% depression from a baseline of 0.75 delta pH unit/h (drawn prior to deployment to Iraq).[1] After 2 days of observation and supportive care, they were allowed to convalesce for the ensuing 2 weeks and subsequently returned to duty.

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[1] The conversion method was established by the US Army Center for Health Promotion and Preventive Medicine.

Table 1
Neuropsychological Testing assessment results 8 months after exposure.

	Score		Score
Intelligence/achievement/effort		**Attention and executive function**	
WAIS-III Full Scale IQ	100	Auditory consonant trigrams-9″ T	40
Verbal IQ	95 (VCI = 105)	18″ T	**38**
Performance IQ	106	36″ T	**34**
Processing speed index	**86**		
WRAT-III Reading	103	WAIS-III Subtest Scaled-Arithmetic	**6**
		Digit span	8
Word memory test	Type I	Seashore rhythm	51
Psychomotor		**Trail making test *T*-scores**	A: 53; B: 54
Finger tapping *T*-scores	43 (R); 54 (L)	Wisconsin card sort categories (raw)	6
		FTMS (raw)	0
Grooved pegboard *T*-scores	**32 (R); 29 (L)**	CVLT trial 1 (raw)	**4**
Language		**Memory**	
Boston naming (60 item) *T*-score	51	Wechsler memory scale-III	
		Logical memory *T*-scores	LMI: 55; LMII: 55
		Visual reproduction *T*-scores	VRI: 42; VRII: 48
Thurstone verbal Fluency *T*-score	**39**	Rey complex figure recall *T*-scores	3′: 43; 30′: 42
Visuoperceptual		CVLT Trail 2 *z*-scores	SDFR: −1.0; LDFR: 0.5
Rey complex figure copy (raw)	33/36		
Hooper visual organization (raw)	28/30		

Note: Impairments/inefficiencies in this individual are bold; WAIS-III = Weschler Adult Intelligence Scale, 3rd edition; WRAT-III = Wide Range Achievement Test, 3rd edition; CVLT = California Verbal Learning Test; SDFR = short delay free recall; LDFR = long delay free recall; LM = logical memory I & II; VR = visual reproduction I & II; FTMS = failure to maintain sets.

Despite subjective fatiguability, the patient continued to serve as an EOD expert without problems. His unit returned to the U.S. 3 months after his exposure. No testing of butylcholinesterase levels was performed, but 1-month following exposure, RBC-ChE activity was normal. Gradually over the 2 months following his return, he began to complain of progressively worsening short-term memory loss, dyscoordination and episodic imbalance, none of which objectively limited his performance. Eight months later, following a non-diagnostic neurological and neurophysiological evaluation in his hometown, he was sent to our tertiary care center for its PET, EMG, and neuropsychological testing capabilities.

He complained of short-term memory loss, mostly involving names and tasks that he intended to complete. He also noted episodic dyscoordination and imbalance. He had fallen several times for no reason and would weave down straight hallways on occasion. These episodes would occur without any precipitating factors. He had not experienced any weakness, numbness or tingling.

He complained of headaches that were post-exertional and mild. He denied any constitutional symptoms, malaise, nausea, vomiting, or diarrhea. He denied any difficulties with swallowing, speaking, or double vision. He admitted to some difficulty with sleep, but denied mood changes or lability, irritability, or personality changes. He had no significant past history except for sinus, hemorrhoid, and arthroscopic knee surgery. There was no significant family history. He denied tobacco, alcohol, or illicit drug use. He was a father of one healthy child. He took no medications.

On physical examination, he was a well-developed, well-nourished male in no acute distress. His vitals were stable. He was well-groomed and his mood appeared good and his affect was full.

On neurological examination, he was fully oriented and his language was normal. His cranial nerve examination was unremarkable. His motor, reflex, sensation, and gait examinations were normal, but he had some difficulty with rapid alternative finger-tapping. He was not able to recall one of three words at 3 min, but was able to with prompting. He was only able to recall six digits in a forward sequence and four in reverse (low for age). He was only able to name 11 words beginning with the letter "F" in 1 min (low for age), and could only remember five words of a nine-word list without any improvement with up to three repetitions (impaired).

Basic chemistry, hematology and toxicology screens were negative. MRI examination of the brain and spine was normal, and electromyography/nerve conduction was normal. Electroencephalography and positron emission tomography (PET) were normal. His neuropsychological test demonstrated a mild cluster of impairments (Table 1). Despite full effort, he demonstrated reduced speed of information processing (Wechsler Adult Intelligence Scale [WAIS] Processing Speed Index [PSI] subtest) and poor focused and divided attention (Auditory Consonant Trigrams (ACT) and the Trial 1 of the California Verbal Learning Test [CVLT]). Testing also revealed difficulty in speeded, bilateral manual motor coordination (grooved pegboard test). While his problem solving, mental flexibility, naming, new learning, recall, and visuoperceptual integration was normal, he showed delays on timed tasks that required rapid mental processing of information. Certain aspects of attention were affected, with greatest impairment on divided attention tasks. Finally, results of the Minnesota Multiphasic Personality Inventory (MMPI-2, a test for psychopathology) did not reveal the presence of significant emotional distress or any significant mood, anxiety, or thought disorder. Further, it validated the results of his neuropsychological testing.

3. Discussion

There have been few reports on the long-term neurologic sequelae of acute sarin exposure. The few clinical observations in humans are limited to post-exposure victims of the Tokyo subway attack. A delayed cerebellar syndrome and has been described (Yokoyama et al., 1998), in which exposed patients demonstrated an increased postural instability as documented by computerized posturography. Cognitive deficits in the Tokyo subway victims are mostly limited to descriptions of impairment in working memory such as backward digit span, which was observed to be persistent in up to 3 years (Nishiwaki et al., 2001).

The cognitive deficits in our patient demonstrated reduced information processing speed, poor focused and divided attention, and difficulty in speeded, bilateral manual motor coordination. He performed abnormally in the ACT, the CVLT, the WAIS-PSI, and the grooved pegboard test. The ACT task measures divided attention and information processing ability by requiring the individual to

count out loud backwards for a specified delay period and then recall a consonant trigram that was verbally given to them prior to the delay period (Spreen and Strauss, 1998). The CVLT is a measure of new verbal learning and recall in which a series of 16 words are presented over five learning trials and the individual is later required to produce those words after a distraction task and a longer delayed period. The Trial 1 score is an indicator of the individual's ability to attend novel information without repetition (Spreen and Strauss, 1998). The WAIS (3rd edition) is a measure that provides information on the individual's overall intellectual abilities and identifies areas of potential intellectual weakness or disability. The PSI subtest is a measure of one's ability to quickly and accurately process and act on visual information (Kaufman and Lichtenberger, 1999). The grooved pegboard test measures manual fine motor speed and coordination by requiring the patient to rapidly place small metal pegs into alternating slotted holes of alternating positions on a board (Lezak, 1995). These deficits are similar in nature to those present in US soldiers exposed to sarin during the 1991 Gulf War (Proctor et al., 2006).

The entire body of medical literature describing the neuroanatomical and neuropathological substrate of long-term sarin effects is composed solely of experimental studies in the animal model. These have demonstrated that there may be permanent alterations in the density of cholinergic receptor subtypes after subclinical sarin exposure. These changes may be a potential mechanism by which memory dysfunction can result from sarin (Henderson et al., 2001).

Behavioral changes following low-level sarin exposure have been described, though the evidence for delayed or long-term effects is discordant. In one study, rats exposed to sarin showed behavioral abnormalities, specifically decreased open field exploration and increased acoustic startle that persist despite normalization of cholinesterase dysfunction up to 16 weeks post-exposure (Scremin et al., 2003). However, acute and repeated low levels of sarin can impair rat spatial memory acutely, but this resolves 3 weeks after exposure (Kassa et al., 2001). Several studies have demonstrated persistent EEG changes up to 1 year after exposure (van Helden et al., 2004). In non-human primates, however, acute or delayed behavioral changes have not yet been correlated to levels of RBC-ChE inhibition similar to that seen in our patient. Acute, low-level sarin exposure in monkeys did not impair their cognitive performance on several cognitive tasks (Pearce et al., 1999; Genovese et al., 2007).

Pathologically, Wallerian degeneration as well as neuronal apoptosis is seen in chronic exposure, while higher acute doses of sarin increase the permeability of the blood–brain barrier. Selective injury is seen in the thalamus, piriform cortex and hippocampus as well as degeneration of cerebellar Purkinje cells (Abou-Donia, 2003; Abdel-Rahman et al., 2002; Kadar et al., 1995). Proposed mechanisms of these degenerative pathways include decreases in endothelial barrier antigen (EBA) and microtubule-associated protein (MAP-2). The clinical relevance of the cerebellar involvement may explain the delayed-onset ataxia syndrome that was first described in the Tokyo subway victims (Yokoyama et al., 1998). Human observations of delayed morphological changes following acute sarin exposure have demonstrated quantifiable reduction in both overall white matter volume and hippocampal volume, a memory-encoding structure well-known to inter-relate with cholinergic brain centers (Heaton et al., 2007; Yamasue et al., 2007).

In summary, this is the first human sarin exposure documented since the 1995 Tokyo subway incident and the first US sarin battlefield casualty. We are not aware of other reports of exposure during the ongoing conflict in the Middle East. Although there is no way to exclude the possibility of a sole or concurrent psychiatric component, our patient neither endorsed subjective complaints suggestive of PTSD nor exhibited any objective evidence as assessed by neuropsychometrics. Although the neuropsychological battery administered is accepted as a valid and reproducible measure, there is some inherent margin of error for what is considered a deviation from the norm. In addition, conclusion of a causal relationship between sarin exposure and his subtle deficits is not substantiated, though his deficits do suggest the possibility of long-term organic brain dysfunction despite normalization of RBC-ChE activity. Interestingly, his impairments tended to be more apparent on tests of motor tasks and attention, both reliant on cholinergic neurotransmission. Since animal experiments implicate an effect of sarin on various neuroanatomical structures that are integral to memory and attention, a similar mechanism could occur following exposure in humans. The advent of higher resolution imaging techniques and functional mapping such as fMRI may help define the neuroanatomical substrate of the post-sarin syndrome as a future topic of study.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

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