Management of Nerve Agent Exposure: A comprehensive Guide for Neurologists

Leila Fettah, Fazia Berraj, Hamza Djerra, and Khirreddine Bouchouareb.

Abstract— **This review serves as a comprehensive resource for neurologists, equipping them with the necessary knowledge to manage cases of nerve agent exposure, specifically for crime scene technicians and responders at highly contaminated crime scenes, including the latest developments in toxic agents such as Novichok. Nerve agents like Sarin and VX inhibit acetylcholinesterase, triggering acute cholinergic crises with symptoms such as seizures, respiratory failure, and cardiovascular collapse. The review highlights key treatment protocols involving atropine, pralidoxime, and benzodiazepines, while addressing both acute and long-term neurological sequelae. It emphasizes the importance of preparedness, focusing on new agents and the need for neurologists to be fully equipped to respond to these life-threatening situations.**

Keywords— **Nerve agents, neurological preparedness, cholinergic crisis, clinical pathway, antidotes, highly contaminated crime scenes.**

I. INTRODUCTION

Nerve agents, a particularly lethal class of chemical warfare agents, have been deployed in various conflicts and acts of terrorism. Developed initially in the 1930s, these agents continue to pose a grave threat. High-profile incidents, such as the sarin gas attack in Tokyo and the Novichok poisoning of Sergei Skripal, underscore the persistent danger these compounds represent to public health and safety [1].

Military organizations around the world are actively preparing for scenarios involving chemical warfare, including the use of nerve agents, through the establishment of intervention groups specialized in nuclear, radiological, biological, and chemical (NRBC) threats. For instance, the recent designation of the National Institute of Criminalistics and Criminology of National Gendarmerie (NICC/NG) to integrate the network of laboratories capable of analyzing such toxic compounds highlights the growing global awareness of the threat posed by these agents at a national level [2]. Alongside military preparedness, it is essential for national healthcare systems to develop rapid-response capabilities to manage mass casualties resulting from chemical warfare [3]. Neurologists, in particular, play a critical role in such scenarios. They must be equipped with the knowledge to recognize and treat the complex neurological effects of nerve agent poisoning, both in acute and long-term phases [4]. This article aims to explore the toxicology, pathophysiology, diagnosis, and treatment of nerve agents, with a particular focus on their impact on the central and peripheral nervous systems (PNS). Preparedness at the neurological level is key to mitigating the devastating consequences of nerve agent exposure, as early recognition and intervention can be the difference between life and death in these high-stakes scenarios.

II. PHYSICOCHEMICAL PROPERTIES OF NERVE AGENTS

By exhibiting distinct physicochemical proprieties influence their behavior and toxicity, the nerve agents or otherwise the organophosphorus compounds, like Sarin (GB), Soman (GD), Tabun (GA), VX, and newer agents like Novichok, affects the dispersal and the potential for exposure which contribute to the mechanism of action as potent acetylcholinesterase (AChE) inhibitors. These volatile liquids disrupt the normal function of acetylcholinesterase (AChE), an enzyme vital for nerve signal transmission by breaking down acetylcholine [1][5]. The key physicochemical characteristics of these agents include their volatility, boiling points, and persistence in the environment are presented in Table I.

Table I
Physicochemical properties of common nerve agents (Sarin, Soman, VX, and Novichok) [1] [5].

Property	Sarin (GB)	Soman (GD)	VX	Novichok
Boiling Point (°C)	158	198	298	Not fully known
Vapor Pressure (mm Hg)	2.1 at 20°C	0.4 at 25°C	0.0007 at 20°C	Variable
Density (g/mL)	1.10	1.02	1.008	Not fully known
Volatility (mg/m³)	22,000 at 25°C	3,900 at 25°C	10.5 at 25°C	Highly potent

III. NEUROLOGICAL EFFECTS OF NERVE AGENTS

A. Mechanisms of acetylcholinesterase inhibition

Nerve agents exert their toxic effects primarily by inhibiting acetylcholinesterase (AChE), an enzyme that plays a pivotal role in terminating synaptic transmission by hydrolyzing acetylcholine into choline and acetic acid. Normally, acetylcholine is released from the presynaptic neurons into the synaptic cleft, where it binds to cholinergic receptors on postsynaptic membranes to propagate nerve signals. Once the signal has been transmitted, acetylcholinesterase rapidly degrades acetylcholine, thus halting its activity and preventing overstimulation of cholinergic receptors [6].

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Nerve agents like Sarin (GB), VX, and Novichok act by forming a covalent bond with the active serine site of acetylcholinesterase, effectively "phosphorylating" the enzyme, rendering it unable to break down acetylcholine [7]. This phosphorylation is generally irreversible, particularly without timely intervention with antidotes such as oximes, which can cleave the bond and restore AChE function. As acetylcholine continues to accumulate unchecked at cholinergic synapses, overstimulation occurs at both nicotinic and muscarinic receptors throughout the nervous system [8].

Muscarinic receptor overstimulation leads to the classical "cholinergic crisis," with symptoms such as bronchoconstriction, increased bronchial secretions, miosis (pupil constriction), bradycardia, and excessive salivation [9]. On the other hand, nicotinic receptor overstimulation causes fasciculations, muscle weakness, and eventually paralysis, including the paralysis of the diaphragm, which can result in respiratory failure if left untreated [10].

The rapidity of AChE inhibition by nerve agents varies with the specific agent involved. For example, soman (GD) binds particularly quickly to acetylcholinesterase, with an aging half-life of around 2 minutes, while VX, though the most toxic of the agents, has a much longer aging time, allowing for a larger therapeutic window if treated early. Once the "aging" process occurs, the AChE-phosphorylated complex becomes irreversible, leaving no possibility for reactivation by antidotes like pralidoxime (2-PAM) [11].

This irreversible inhibition of acetylcholinesterase ultimately leads to widespread neurological dysfunction, resulting in seizures, loss of consciousness, and status epilepticus—a prolonged seizure condition that is difficult to manage and often fatal without prompt intervention. The pathophysiological effects extend beyond the nervous system, affecting multiple organ systems due to the ubiquitous role of acetylcholine in both the central and peripheral nervous systems (PNS) [12].

B. Impact on the central and peripheral nervous systems

Nerve agents have a profound and devastating effect on both the central and peripheral nervous systems (PNS), primarily through the inhibition of acetylcholinesterase (AChE), an enzyme crucial for terminating the action of acetylcholine in synaptic transmission. The irreversible binding of nerve agents to AChE results in the continuous accumulation of acetylcholine at cholinergic synapses. This leads to overstimulation of both muscarinic and nicotinic receptors, which are responsible for regulating critical physiological functions. The cholinergic crisis that ensues causes a cascade of systemic effects [13][14]. The Fig.1 illustrates this mechanism of action, highlighting how nerve agents disrupt synaptic transmission.

In the central nervous system (CNS), the overstimulation of cholinergic pathways leads to severe neurological manifestations such as seizures and loss of consciousness. Prolonged seizures (status epilepticus) are particularly dangerous as they can result in neuronal damage, potentially leading to long-term cognitive impairments and memory loss. This hyperactivation of the CNS can also lead to disruptions in autonomic regulation, further complicating the clinical presentation with disturbances in blood pressure and heart rate. Seizures may be difficult to control without prompt administration of anticonvulsants, as well as muscarinic antagonists like atropine, and failure to intervene early can result in irreversible brain damage [16].

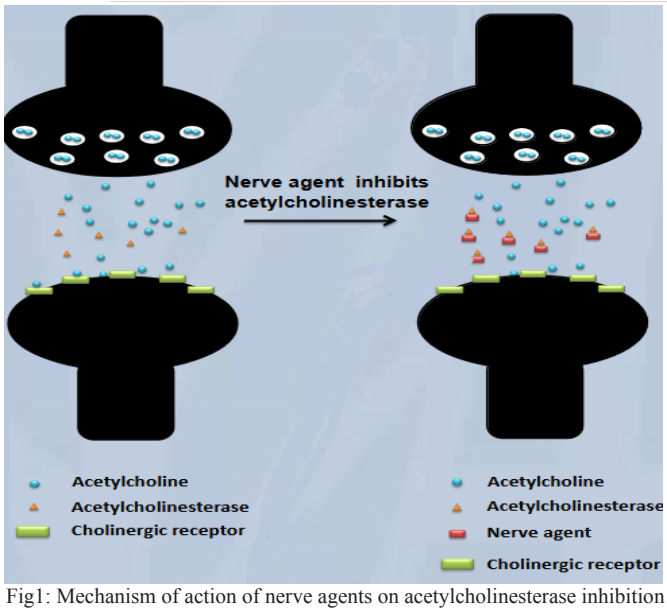


Fig1: Mechanism of action of nerve agents on acetylcholinesterase inhibition [15].

In the peripheral nervous system (PNS), both muscarinic and nicotinic receptors are overstimulated. Muscarinic receptor overstimulation manifests through bronchoconstriction, excessive salivation, lacrimation, bradycardia, and gastrointestinal symptoms such as vomiting and diarrhea. These effects can progress rapidly to life-threatening complications, including severe bronchoconstriction and bronchorrhea, which can block the airways and lead to asphyxiation [13], [17].

Nicotinic receptor overstimulation, on the other hand, primarily affects skeletal muscles, leading to involuntary muscle fasciculations followed by flaccid paralysis. Paralysis of the diaphragm and intercostal muscles impairs respiratory function, leading to respiratory arrest. Without rapid intervention, respiratory failure is the leading cause of death in nerve agent poisoning. The paralysis is a result of sustained depolarization of neuromuscular junctions, which prevents the muscles from relaxing, ultimately causing respiratory muscles to become immobile [18].

The vascular and cardiac systems are also affected. Tachycardia is often seen early due to the nicotinic effects stimulating adrenal release of catecholamines, but as muscarinic overstimulation progresses, bradycardia can dominate, complicating the clinical management further. The combination of respiratory failure and bradycardia increases the risk of hypoxia, which exacerbates neurological damage [19].

Neurologically, the overstimulation of receptors leads to cognitive impairment, with symptoms such as confusion, agitation, and eventually coma. In cases where patients survive the acute phase of poisoning, long-term neurological sequelae are common. These include chronic fatigue, memory deficits, motor dysfunction, and psychiatric disturbances such as anxiety and depression [20].

Thus, nerve agents exert a dual assault on the nervous system by disrupting both central and peripheral cholinergic neurotransmission. The interplay of muscarinic and nicotinic receptor overstimulation underlies the complex and often fatal symptomatology of nerve agent exposure. Prompt identification and intervention are crucial to mitigate the risk of death from respiratory arrest and to manage the neurological consequences of exposure [13].

C. Symptoms and signs of exposure

Acute exposure to nerve agents presents a distinct pattern of symptoms caused by the accumulation of acetylcholine due to acetylcholinesterase inhibition. This condition triggers overstimulation of muscarinic and nicotinic receptors, leading to a rapid cholinergic crisis. Muscarinic effects manifest as miosis (pupil constriction), rhinorrhea (runny nose), bronchospasm, and increased salivation. Nicotinic receptor stimulation, on the other hand, causes muscle fasciculations, which may progress to paralysis. If untreated, patients may experience seizures, loss of consciousness, and ultimately respiratory failure due to the paralysis of the diaphragm and central apnea [6][21].

The symptoms and life-threatening consequences of nerve agent exposure can be summarized in the following Table II.

Table II

Summary of symptoms and life-threatening consequences of nerve agent exposure [1][14].

Category	Symptoms and Signs	Life-threatening Consequences
Muscarinic Effects	Miosis (pupil constriction), rhinorrhea (runny nose), bronchospasm, increased salivation	Overstimulation of muscarinic receptors
Nicotinic Effects	Muscle fasciculations progressing to paralysis	Paralysis, particularly of the diaphragm, leading to respiratory failure
Respiratory Failure	Bronchorrhea (excessive mucus), bronchoconstriction leading to respiratory distress	Severe respiratory failure, often fatal without intervention
Seizures	Seizures, status epilepticus (resistant to treatment)	Increased risk of death, can lead to central apnea
General	Rapid onset of symptoms (inhalation exposure), slower onset for dermal exposure	Death within minutes without rapid intervention, respiratory arrest

Bronchorrhea, which refers to excessive mucus secretion in the airways, combined with bronchoconstriction, severely compromises respiratory function, creating a scenario akin to a severe asthma attack. These symptoms, particularly bronchorrhea, can contribute significantly to respiratory failure, a leading cause of death in cases of nerve agent poisoning. The onset of seizures further exacerbates the risk of mortality, as they can lead to status epilepticus, a condition that is particularly resistant to treatment due to the widespread activation of cholinergic synapses throughout the brain [18].

In the absence of rapid intervention, nerve agent exposure can lead to death within minutes. The severity of symptoms often correlates with the dose and route of exposure. For example, inhalation exposure typically results in quicker onset of symptoms, such as miosis, rhinorrhea, and respiratory distress, whereas dermal exposure may present more slowly, depending on the absorption rate [14],[18].

Overall, early recognition and intervention are critical to prevent fatal outcomes, especially respiratory arrest, which remains the most immediate life-threatening consequence of nerve agent exposure. Rapid decontamination and the administration of atropine, pralidoxime, and anticonvulsants such as benzodiazepines remain the cornerstone of treatment in these acute settings.

IV. ASSESSMENT OF CLINICAL MANIFESTATIONS AND DIAGNOSIS CHALLENGE

A. Clinical presentation

Patients exposed to nerve agents typically exhibit a cholinergic toxidrome, a constellation of symptoms due to excessive acetylcholine activity at muscarinic and nicotinic receptors. The hallmark features include miosis (constricted pupils), excessive salivation, lacrimation (tear production), urination, defecation, gastrointestinal distress, and emesis, collectively referred to as the SLUDGE syndrome. This pattern of symptoms is directly related to the overstimulation of muscarinic receptors [22][23].

In cases of severe exposure, patients may progress to experience seizures, bronchorrhea (excessive bronchial secretions), and respiratory failure due to both central apnea and diaphragm paralysis, the latter caused by overstimulation of nicotinic receptors at the neuromuscular junction. The excessive bronchial secretions and bronchoconstriction result in respiratory distress, contributing to the high mortality rates if left untreated. Neuromuscular effects such as fasciculations (involuntary muscle twitching) and eventual flaccid paralysis are also common as the nicotinic receptor overstimulation worsens [18][24].

Initial symptoms often manifest within minutes following exposure, particularly in the case of inhalation exposure, where the onset of symptoms can be almost immediate. Patients may develop rhinorrhea (runny nose), bronchospasm, dyspnea, and a tight chest feeling due to bronchoconstriction and bronchorrhea. The rapid accumulation of acetylcholine can also lead to confusion, agitation, and, in severe cases, coma [25].

In dermal exposure cases, symptoms can be delayed for several hours. A lethal dose of liquid nerve agent on the skin may take up to 30 minutes to manifest fully. Systemic signs often begin with localized diaphoresis and fasciculations, followed by gastrointestinal symptoms, and eventually, central nervous system involvement, including seizures [26].

Without prompt medical intervention, death from nerve agent exposure typically results from respiratory failure. This can occur due to a combination of bronchorrhea, bronchospasm, and flaccid paralysis of the respiratory muscles.

B. Diagnostic challenges

Diagnosing nerve Diagnosing nerve agent poisoning presents several challenges, particularly in mass casualty situations and low-resource environments. These agents often produce rapid and severe effects, which can complicate immediate assessment, and delay in diagnosis significantly worsens patient outcomes. Clinicians must rely heavily on the recognition of clinical signs and symptoms in the acute phase, such as the characteristic cholinergic toxidrome, which includes excessive salivation, miosis, bronchorrhea, muscle fasciculations, seizures, and potentially fatal respiratory failure. In these high-stress scenarios, the rapid identification of the cholinergic syndrome is crucial for initiating life-saving interventions, such as the administration of atropine and pralidoxime, before confirmatory diagnostic tests are available.

In addition to clinical observation, definitive laboratory confirmation of nerve agent poisoning is primarily based on the measurement of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity levels in blood samples [27][28]. Nerve agents inhibit both AChE and BChE, and

reduced enzyme activity is a hallmark of exposure. While AChE is traditionally targeted due to its central role in nerve function, BChE activity has emerged as an important biomarker, particularly in forensic and retrospective analyses. BChE is abundant in plasma and binds more readily with nerve agents than AChE, making it a valuable marker for longer-term detection [29]. However, measuring AChE and BChE levels can be complex and requires specialized equipment, which may not be available in all settings, particularly in field or emergency situations. Therefore, AChE and BChE activity assays are often used retrospectively, meaning the clinical diagnosis must be made rapidly based on symptomatic presentation.

Another diagnostic tool is the detection of nerve agent metabolites, such as organophosphate metabolites, in biological fluids like blood and urine [30]. These assays are agent-specific and can provide more detailed information about the type of nerve agent involved. Importantly, assessing these metabolites in the environment is also crucial to prevent additional cases of exposure. Environmental monitoring helps detect residual contamination and supports containment efforts, reducing the risk of secondary exposures in the aftermath of a chemical attack. Both biological and environmental sample processing and analysis methods must be capable of handling a high throughput of samples, given the potential volume in mass casualty scenarios [30][31]. While this method offers valuable forensic and epidemiological data, it also has limitations in real-time clinical management, as it requires sophisticated laboratory resources that may not be immediately accessible in the chaotic environment of a chemical attack.

In mass casualty incidents, where multiple patients present with overlapping symptoms from potential exposures to various toxicants, the situation becomes even more complex. Symptoms of nerve agent poisoning can mimic those of other chemical exposures, such as organophosphate insecticides or even certain pharmaceutical overdoses, leading to diagnostic confusion. Moreover, the latency of symptom onset, particularly with dermally absorbed agents like VX, complicates the initial clinical assessment, as symptoms may develop hours after exposure [32].

The severity of the exposure, the route of administration (inhalation, ingestion, or dermal absorption), and individual patient factors, including age and comorbidities, also contribute to the variability of clinical presentation, further complicating the diagnostic process. In cases of dermal exposure, the delayed appearance of symptoms can mask the onset of a potentially fatal cholinergic crisis until it is too late [13].

Given these challenges, effective diagnosis often requires a multifaceted approach that includes clinical acumen, rapid deployment of diagnostic tools where available, and an understanding of the environmental context. Medical personnel must be trained to recognize the subtle early signs of nerve agent exposure and have protocols in place for immediate treatment initiation based on clinical suspicion alone, even before laboratory confirmation is possible [33].

C. Acute and Long-Term Management of Nerve Agent Exposure: Clinical Implications and Neurological Sequelae

In the immediate phase following nerve agent exposure, rapid medical intervention is crucial to prevent mortality, particularly due to the severe cholinergic crisis induced by acetylcholinesterase inhibition. Without timely intervention, the excessive accumulation of acetylcholine at neuromuscular junctions leads to respiratory failure caused by paralysis of the diaphragm and other muscles essential for breathing. Acute management typically involves the administration of antidotes such as atropine, which blocks muscarinic acetylcholine receptors, and pralidoxime (2-PAM), which reactivates acetylcholinesterase, provided it is administered promptly. The use of benzodiazepines is recommended for controlling seizures, a common complication of acute nerve agent poisoning [34].

The long-term phase of nerve agent poisoning often involves persistent neurological deficits, which may manifest as cognitive impairment, motor dysfunction, and chronic fatigue. These effects are primarily associated with survivors of high-level exposure. Cognitive deficits, such as memory impairment, reduced attention, and difficulty with abstract thinking, have been reported even in individuals who have fully recovered from the acute effects of the poisoning. Motor deficits may include weakness, tremors, and difficulties with coordination, often attributed to the prolonged overstimulation and subsequent damage to neural circuits [34].

Psychiatric conditions are also frequently observed in the long-term phase. Anxiety, depression, and irritability are common, with some patients exhibiting signs of post-traumatic stress disorder (PTSD) after exposure to nerve agents, particularly in situations involving mass casualties such as the Tokyo subway sarin attack. These psychiatric sequelae often complicate the recovery process, requiring multidisciplinary care that addresses both the neurotoxic and psychological impacts of the exposure [35].

Long-term follow-up of nerve agent poisoning survivors is essential for the early identification and management of these persistent sequelae. Neurologists play a key role in monitoring cognitive and motor functions, as well as in providing supportive care for psychiatric disorders that may arise post-exposure. Regular neuropsychological assessments are recommended to detect subtle changes in cognitive function that might not be apparent through standard neurological examinations [36].

V. TREATMENT PROTOCOLS

This section outlines the critical steps in managing nerve agent exposure, covering pre-medication, post-exposure treatment, acute management, and long-term care. Fig.2 is a visual representation of the clinical pathway summarizing the key steps of diagnosis, decontamination, and treatment, provided below to guide healthcare professionals through the structured approach required in these emergencies. It highlights the steps from initial diagnosis, decontamination, acute medical management, continuous monitoring, and long-term follow-up in cases of nerve agent poisoning [37].

A. Pre-medication (prevention)

In military settings, the administration of pyridostigmine bromide as a pre-treatment has proven crucial for protecting personnel against nerve agents, particularly soman, a rapidly aging agent that presents unique challenges in traditional antidote treatment. Pyridostigmine is a reversible acetylcholinesterase (AChE) inhibitor that temporarily binds to a fraction of AChE, thus protecting it from the irreversible inhibition caused by nerve agents. The military began using pyridostigmine in the late 1980s when concerns over rapidly aging nerve agents increased, especially during the Iraq-Iran war, where soman production was feared [38].

Animal studies demonstrated that pyridostigmine significantly increased the protective ratio against soman from 1.6 to 40 when combined with standard treatments like atropine and oximes such as pralidoxime. Based on these findings, the U.S. Food and Drug Administration (FDA) authorized pyridostigmine's use under a special waiver during the 1991

Gulf War, making it a standard prophylactic measure for over 100,000 soldiers [39].

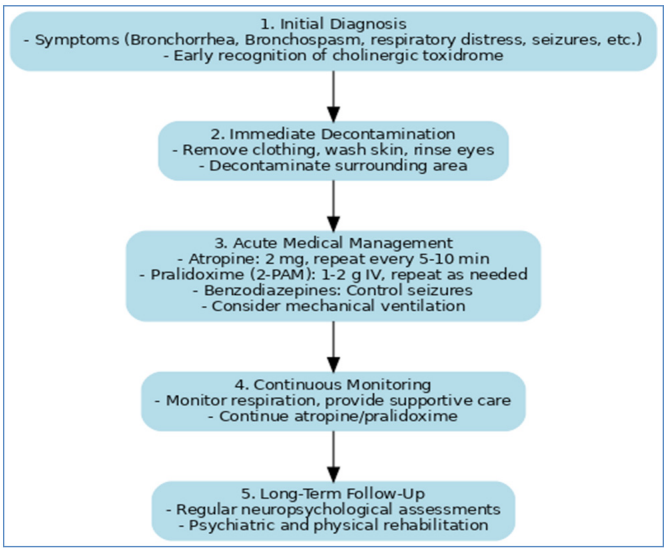


Fig 2 : Clinical pathway for nerve agent exposure management [40].

Typically, a dose of 30 mg every eight hours is prescribed for pre-treatment, starting several hours before potential exposure. The effect of pyridostigmine is to convert a potentially lethal exposure into a manageable medical emergency where standard antidotes can effectively reverse the cholinergic effects [41]. However, it is important to note that pyridostigmine is strictly a pre-treatment and should not be administered after exposure, as it does not offer therapeutic benefits once a nerve agent has bound irreversibly to AChE.

Although pyridostigmine bromide has been an effective battlefield countermeasure, its use has remained largely confined to military contexts. Civilian applications have been limited, with few emergency response agencies adopting it as part of their chemical incident protocols. Further research into pyridostigmine and related protective measures remains essential to expanding its use beyond military operations to civilian first responders [42].

B. Post-exposure treatment

The immediate and effective treatment of nerve agent exposure is crucial for patient survival and minimizing long-term neurological damage. The cornerstone of post-exposure treatment is atropine, an antimuscarinic agent that acts by competitively inhibiting acetylcholine at muscarinic receptors, thereby alleviating the parasympathetic overstimulation caused by nerve agents. Atropine primarily addresses symptoms such as bronchoconstriction, excessive salivation, and bradycardia, which are hallmark signs of muscarinic receptor overstimulation. However, atropine does not reverse the nicotinic effects, such as muscle fasciculations and paralysis, which are critical in respiratory failure and seizure activity associated with nerve agent toxicity [23].

Pralidoxime (2-PAM) is an essential adjunct to atropine in nerve agent poisoning, as it reactivates acetylcholinesterase (AChE) by binding to the phosphorylated enzyme and restoring its function, particularly if administered before the enzyme undergoes "aging" — a process where the nerve agent-enzyme bond becomes irreversible. Pralidoxime is especially effective in reversing the paralysis of respiratory muscles and mitigating the nicotinic effects of nerve agents, such as muscle twitching and diaphragm paralysis. Early administration of pralidoxime is critical, as agents like soman can "age" AChE within minutes, rendering pralidoxime ineffective [34].

While atropine targets muscarinic receptors and pralidoxime regenerates AChE, the concurrent use of benzodiazepines is recommended to control seizure activity, which is a severe complication in nerve agent exposure. Seizures are thought to result from GABAergic dysfunction, exacerbated by the excessive cholinergic activity, and are life-threatening if not promptly controlled. Therefore, treatment protocols often include the administration of diazepam or midazolam to manage convulsions, which are frequently seen in severe cases of poisoning [37].

In mass casualty situations, the Mark I NAAK (Nerve Agent Antidote Kit) or DuoDote® autoinjectors, combining atropine and pralidoxime in pre-measured doses, are used for rapid intramuscular administration in both civilian and military settings. These autoinjectors are designed for easy use in the field and allow for immediate intervention, even before professional medical care is available. Studies have shown that timely administration of these antidotes significantly improves survival rates and reduces the long-term neurological sequelae associated with nerve agent exposure [34].

C. Acute management

Acute management of nerve agent poisoning requires immediate action to preserve respiratory function and control seizures. Nerve agents disrupt normal neurotransmission by inhibiting acetylcholinesterase (AChE), leading to a cholinergic crisis characterized by convulsions and respiratory failure. The rapid use of benzodiazepines, such as diazepam, is critical for controlling seizures that arise from the overstimulation of nicotinic and muscarinic receptors. Diazepam, administered intramuscularly or intravenously, has been shown to be effective in managing status epilepticus, the most severe form of convulsive seizures associated with nerve agent exposure [20].

Atropine is the cornerstone of treatment for counteracting the excessive muscarinic effects of nerve agents, including bronchoconstriction, excessive secretions, and bradycardia. Atropine works by competitively inhibiting acetylcholine from binding to muscarinic receptors. For severe cases, large doses of atropine may be required, and treatment must continue until secretions dry, bronchospasms resolve, and respiratory function improves. In clinical settings, atropine is often administered in repeated doses of 2 mg every 5 to 10 minutes until breathing normalizes, with no maximum cumulative dose for nerve agent exposure [37].

Pralidoxime (2-PAM), an oxime, is administered in conjunction with atropine to reverse the inhibition of AChE by reactivating the enzyme. Pralidoxime is particularly effective when given early in the poisoning event, as it can displace the nerve agent from AChE before "aging" occurs— a process in which the bond between the agent and the enzyme becomes irreversible. A typical pralidoxime dose is 1 to 2 grams intravenously over 20-30 minutes, repeated as necessary to relieve muscle weakness and improve neuromuscular function [21].

Supportive care, especially mechanical ventilation, is crucial for patients experiencing respiratory failure due to diaphragm paralysis. Mechanical ventilation should be initiated early, even before the tidal volume falls significantly, to prevent hypoxemia and respiratory arrest. This is especially important because blood gas measurements may not predict imminent respiratory failure in these patients. Additionally, airway management is essential, and suctioning may be required due to copious bronchial secretion [37].

D. Antidotes: atropine and pralidoxime

Atropine remains the cornerstone of treatment for nerve agent poisoning, particularly in managing the muscarinic effects. It works by competitively inhibiting acetylcholine at postsynaptic muscarinic receptors, thus mitigating life-threatening symptoms such as bronchospasm, excessive secretions, and bradycardia. However, atropine has no effect on nicotinic receptors, which are responsible for skeletal muscle paralysis—a critical component of nerve agent toxicity [23].

The effectiveness of atropine is dose-dependent, and there is no maximum recommended dose for nerve agent exposures. The standard adult dose begins with 2 mg administered either intravenously (IV) or intramuscularly (IM), with repeated dosing every 5 to 10 minutes until respiratory secretions are adequately controlled and the patient can be ventilated without difficulty. In severe cases, cumulative doses of 10 to 20 mg over several hours may be required to achieve clinical stability. Historical reports, such as those from the Iran-Iraq war, cite doses of up to 200 mg in severely affected soldiers, underscoring the drug's broad therapeutic range and safety profile [43].

Pralidoxime (2-PAM), shown alongside atropine in Fig.3, is an oxime that works by reactivating acetylcholinesterase through cleaving the bond between the enzyme and the nerve agent—provided that this bond has not undergone the irreversible process of "aging." Pralidoxime is particularly effective in reversing nicotinic effects, including muscle paralysis. Early administration of pralidoxime is crucial to reversing the inhibition of acetylcholinesterase, and the standard adult dose is 1-2 grams administered intravenously over 30 minutes, followed by a continuous infusion if necessary. When IV access is not available, pralidoxime can be administered intramuscularly [44].

It is important to note that pralidoxime's effectiveness rapidly diminishes over time due to the aging process of the nerve agent-acetylcholinesterase bond. For instance, soman causes aging within 2 minutes, significantly reducing the window for effective treatment with oximes. In contrast, nerve agents like VX have a longer aging period, allowing for a broader window of therapeutic intervention [35].

Together, atropine and pralidoxime provide a synergistic approach to treating nerve agent poisoning. Atropine addresses the muscarinic symptoms, while pralidoxime reactivates acetylcholinesterase and reverses the nicotinic effects. This combination has become the standard treatment protocol in both military and civilian settings, particularly during mass casualty scenarios [24].

Atropine



https://mms.mckesson.com/product/1184594/International-Medication-Systems-76329334001

Pralidoxime (2-PAM)



https://www.ondrugdelivery.com/

Fig 3: Commercial Forms of Antidotes: Atropine and Pralidoxime (2-PAM).

In addition to the standard treatment protocol with atropine and pralidoxime, a promising enzymatic approach is currently under investigation in animal models. This strategy involves the use of bioscavengers, either stoichiometric or catalytic, which can trap or degrade organophosphates (OPs) effectively. These enzymatic treatments are being tested for their ability to provide safe and efficient decontamination without environmental impact, offering new avenues for prophylaxis and treatment in nerve agent poisoning[45].

E. Decontamination

In cases of exposure to nerve agents, decontamination is a critical step to mitigate further absorption and prevent secondary contamination. Immediate decontamination reduces the systemic absorption of the agent through the skin and prevents re-aerosolization of toxic vapors that may affect others nearby. The recommended procedures include washing the skin with soap and water or a 0.5% sodium hypochlorite (bleach) solution, followed by rinsing with isotonic saline. Soap and water are effective in physically removing the agent, while the bleach solution helps neutralize the organophosphate compounds. Special care should be taken to avoid using bleach solutions near the eyes, as this can cause additional chemical burns [26].

In large-scale exposure incidents, decontaminable gurneys and non-permeable surfaces should be used to prevent recontamination. Contaminated clothing should be removed immediately and sealed in impermeable bags to avoid further exposure. If vapor exposure is suspected without skin contact, clothing removal alone may be sufficient as skin decontamination is not always necessary in such cases. However, vapor can become trapped in the fabric, and thus complete disrobing is crucial. If eye contamination occurs, flushing with water for at least 10 minutes is advised to prevent long-term ocular damage [7].

Patients must be decontaminated before being transported to medical facilities to protect healthcare personnel from secondary exposure. This principle is particularly emphasized during mass casualty events, where rapid decontamination becomes a logistical challenge but is essential to controlling the spread of the agent and ensuring the safety of first responders and medical staff [1].

VI. NEUROLOGICAL SEQUELAE

A. Long-term neurological impairments

Exposure to organophosphorus (OP) nerve agents, such as Sarin, Soman, VX, and Tabun, has been linked to a variety of long-term neurological sequelae. Survivors of acute poisoning by these agents frequently experience subtle but persistent neuropsychological and motor deficits. These deficits, which may last for months or even years, include cognitive impairments, memory loss, chronic fatigue, and motor dysfunctions such as muscle weakness and impaired coordination. Neuropsychological outcomes, in particular, tend to be subtle and may be overlooked without extensive clinical evaluation, often requiring specialized neuropsychological testing [13].

The mechanisms underlying these chronic neurological effects are not fully understood but are believed to involve a combination of direct neuronal damage from acetylcholinesterase (AChE) inhibition and secondary complications like hypoxic encephalopathy due to respiratory failure during acute poisoning. Studies on both humans and animals have reported lasting changes in brain electrical activity, such as alterations in EEG patterns, and histopathological changes like neuronal

degeneration in the hippocampus and cortex. These alterations are particularly prevalent in survivors who experienced seizures or prolonged convulsive activity during the acute phase of poisoning [33].

Some individuals also report persistent psychological symptoms, including mood changes, insomnia, and post-traumatic stress disorder (PTSD), which are often difficult to disentangle from the neurological effects of the poison itself. Though most survivors recover significantly over time, some neurological and psychological impairments may persist long-term, impacting the quality of life [46].

B. Cognitive and motor deficits

Survivors of acute nerve agent poisoning often face a complex array of neurological and neuropsychological deficits. These impairments predominantly manifest as subtle but significant changes in both cognitive functioning and motor coordination. Studies have shown that nerve agents induce prolonged cholinergic crisis, leading to disruptions in brain function and sustained neuromuscular inhibition. For instance, a significant portion of individuals exposed to organophosphate (OP) nerve agents exhibit difficulties with tasks requiring attention, memory, and problem-solving skills. Neuropsychological evaluations have demonstrated that deficits in intellectual functioning, such as slower processing speed and impaired abstraction, may persist for months or even years post-exposure. Additionally, in a cohort of severely poisoned individuals, decreased scores on the Wechsler Adult Intelligence Scale (WAIS) were observed in both Full Scale and Verbal IQ, indicating a measurable decline in cognitive performance [14].

Motor deficits also constitute a prominent feature of the long-term consequences of nerve agent exposure. Survivors frequently experience muscle fasciculations, weakness, and compromised coordination. Motor deficits tend to be associated with the ongoing inhibition of acetylcholinesterase (AChE), which disrupts normal neuromuscular transmission, leading to muscle weakness and difficulties with fine motor tasks. Studies have shown that approximately 24% of individuals with high-level nerve agent exposure present with motor impairments consistent with peripheral neuropathy. Despite the initial severity of these deficits, some degree of recovery can be expected over time, as axonal regeneration occurs slowly, often taking months to years [13].

Additionally, psychiatric sequelae, including depression, anxiety, and irritability, are common among survivors. These neuropsychiatric symptoms, in many cases, overlap with post-traumatic stress disorder (PTSD) and can be attributed to both the direct neurotoxic effects of the agent and the psychological trauma associated with the exposure event. Notably, reports from the survivors of the Tokyo subway sarin attack suggest that cognitive dysfunction, including difficulties with concentration, memory lapses, and mood alterations, persisted for months following recovery. Though full recovery is possible in some cases, many patients continue to struggle with varying degrees of neuropsychological impairment, significantly impacting their quality of life long after the initial exposure [14].

VII. SPECIAL CONSIDERATIONS IN CHILDREN

Children are especially vulnerable to nerve agents due to their smaller body mass, higher respiratory rates, and immature metabolic systems, which increase their absorption of toxic substances. The underdeveloped blood-brain barrier in children allows nerve agents to more easily penetrate the central nervous system, heightening the risk of severe neurotoxic effects like seizures and coma. Their smaller airways and weaker respiratory muscles make them more prone to respiratory failure, a leading cause of death in nerve agent poisoning. Pediatric management requires careful adjustment of antidote doses, particularly with atropine and pralidoxime, and emphasizes rapid respiratory support and seizure control to prevent long-term neurological damage [47].

VIII. EMERGING THREATS: NOVICHOK AGENTS

Novichok agents represent a more recent and concerning class of nerve agents, first developed in the Soviet Union between 1971 and 1993. These agents, whose name translates to "newcomer" in Russian, have been largely unknown to the broader public until recent high-profile cases, such as the 2018 poisoning of Sergei Skripal and his daughter Yulia in Salisbury, UK. Novichok agents are reportedly several times more potent than VX, one of the most lethal nerve agents developed during the Cold War era. According to accounts from Russian scientists involved in their development, these agents were engineered to bypass existing chemical weapon detection systems and antidotes [48].

Novichok agents are organophosphorus compounds, similar in chemical behavior to the V-series and G-series nerve agents. However, their chemical structure is distinct enough to evade standard detection technologies used for these older nerve agents. The severity of Novichok poisoning is amplified by its high persistence in the environment, owing to its low volatility. Unlike more volatile nerve agents such as sarin, which dissipates more quickly in the atmosphere, Novichok remains dangerous for longer periods, especially in liquid form, as demonstrated in the Salisbury case, where multiple secondary exposures occurred [49].

The pathophysiology of Novichok agents mirrors that of other nerve agents by inhibiting acetylcholinesterase (AChE), resulting in the accumulation of acetylcholine at synaptic junctions, which leads to overstimulation of muscarinic and nicotinic receptors. The overstimulation of muscarinic receptors causes symptoms such as miosis, bronchospasm, and excessive salivation, while nicotinic receptor overstimulation leads to muscle fasciculations, paralysis, and eventually, respiratory failure. Novichok's potency means that even minute quantities can be lethal; a few milligrams absorbed through the skin or inhalation can result in death if not treated rapidly [9].

The 2018 Salisbury attack also highlighted the psychological toll on first responders and the local population. Nearly 100 police officers sought psychological support in the aftermath of the incident, with concerns about long-term health impacts from even minimal exposure. Novichok's persistence and the difficulty of decontamination make it a particularly insidious agent. Emergency personnel involved in such incidents must be prepared for both immediate clinical effects and the risk of prolonged environmental contamination [41].

Given the extreme toxicity and persistence of Novichok agents, they present unique challenges in both detection and treatment. Current antidotes, including atropine and oximes like pralidoxime, may have limited efficacy depending on the timing of administration and the degree of exposure. Furthermore, there remains limited publicly available data on the exact chemical composition of Novichok agents, as much of the research surrounding their development is classified. Continued research and international cooperation are necessary to develop more robust detection methods and medical countermeasures to mitigate the threat posed by these advanced nerve agents [5].

IX. CONCLUSION

Nerve agents remain a significant concern in both military and civilian contexts, particularly due to their potential use in terrorist activities. The development of these agents, such as Sarin, VX, and more recently Novichok, has marked a grim evolution in chemical warfare, underlining the need for heightened preparedness among healthcare providers, especially neurologists. These agents cause acute cholinergic crises by inhibiting acetylcholinesterase, which can rapidly lead to fatal outcomes without timely intervention. The rapid onset of symptoms, including seizures, respiratory failure, and cardiovascular collapse, necessitates prompt medical management involving atropine, pralidoxime, and benzodiazepines for seizure control.

Furthermore, the long-term neurological sequelae present an ongoing challenge for survivors, who may experience cognitive impairments, psychiatric disturbances, and motor deficits. Future research must focus on enhancing diagnostic tools and developing more efficient therapeutic strategies to mitigate both the acute and chronic consequences of nerve agent exposure. The adaptability of healthcare systems, including the establishment of robust decontamination protocols and the stockpiling of essential antidotes, is crucial to reducing morbidity and mortality associated with these chemical weapons. Emergency preparedness for nerve agent attacks is essential, particularly through the acquisition of antidote kits. These kits should be obtained as part of broader purchases intended for major disaster preparedness.

A multidisciplinary approach, involving neurology, toxicology, and emergency medicine, is essential to address the complex medical and neurological issues that arise from nerve agent exposure. The role of neurologists is not only crucial for clinical management but also for forensic investigations. Their diagnostic expertise can provide critical evidence of nerve agent exposure, serving as a key element in criminal investigations related to chemical warfare.

In Algeria, as in other nations, the healthcare system must continue to evolve to address the risks posed by these chemical threats. While military preparedness has advanced, the national healthcare infrastructure, including specialized medical training and hospital readiness, should be further strengthened to manage potential nerve agent incidents. This review serves as a reminder and an essential tool for neurologists and emergency medicine specialists, emphasizing the critical knowledge and preparedness they must possess to respond effectively to these life-threatening scenarios. Comprehensive preparedness, rapid-response protocols, and continued improvements in medical infrastructure are key to mitigating the inevitable threat posed by nerve agents in the future.

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