Autoimmune dysautonomia secondary to chronic organophosphate exposure

Sri Harsha Kanuri, MD,* Poojita Shivamurthy, MD,* Rawan Albadareen, MD,† Mehmet Ali Elbey, MD,* Rakesh Gopinathannair, MD, FHRS,* Dhanunjaya Lakkireddy, MD, FACC, FHRS*  

From the *Kansas City Heart Rhythm Institute (KCHRI), Overland Park, Kansas, and †Department of Neurology, Overland Park Regional Medical Center, Overland Park, Kansas.

Introduction
Homeostasis is maintained by the net balance of sympathetic and parasympathetic nervous system through a complex neurohormonal network. Autonomic failure often results in cardiovascular symptoms such as orthostatic hypotension, presyncope, syncope, fluctuation of blood pressure, and cardiac arrhythmias. Long-term organophosphate (OP) exposure is well described in the literature to be associated with 2 syndromes, namely, the intermediate syndrome of OP-induced delayed polyneuropathy and chronic OP-induced neuropsychiatric disorder.1 Although previous studies established a relationship between chronic OP poisoning and neurodegenerative diseases, its possible role in cardiac dysautonomia has not been well considered and studied until now.2

We present a rare clinical scenario wherein a patient exposed to chronic low levels of OP-based pesticides developed autoimmunity and was found to have antibodies against alpha3 (α3) subunit of ganglionic acetylcholine receptors (α3-AChR) with clinical manifestations of dysautonomia, neuropsychiatric symptoms, and peripheral neuropathy.

Case report
A 65-year-old female patient with medical history of hypertension, hyperlipidemia, and hypothyroidism underwent extensive multidisciplinary evaluation at our institution for symptoms involving multiple organ systems suggestive of autonomic failure for few months. Her predominant complaint was “sensation of doom” related to chest tightness, palpitations, and syncopal episodes with a prodrome of nausea and lightheadedness. Aside from these episodes, she also experienced episodic, excessive lacrimation, rhinorrhea, peripheral neuropathy, dizziness, lightheadedness, generalized weakness, and early satiety. Some of these episodes were triggered by eating. The patient also complained of vague chest pain and palpitations. The chest pain was on and off, was nonradiating, and did not have any exacerbating or relieving factors. Chest pain was not associated with shortness of breath or sweating. She exhibited orthostasis and on several occasions had supine systolic blood pressures around 70 mm Hg. The patient was in normal sinus rhythm and she kept fluctuating from sinus bradycardia to sinus tachycardia. Troponin levels were normal. Stress test was negative with no exercise-induced angina, arrhythmias, or ST-segment elevation. Chest angiogram showed no evidence of pulmonary embolism, but showed remote granulomatous disease with heavily calcified middle mediastinal and right lower lobe pulmonary granulomata. Two small noncalcified right middle lobe pulmonary nodules, the largest measuring 3 mm, were noted. She was referred to a pulmonologist for further management of granulomatous disease.

An electrocardiogram performed during her admission into the emergency room revealed normal sinus rhythm.

KEY TEACHING POINTS
- Chronic moderate exposure to organophosphate (OP) pesticides might be associated with underlying autoimmunity.
- Farmers with long-term OP exposure who develop anticholinergic receptor (α3-AChR Ab) autoantibodies against autonomic ganglia might benefit from immunosuppressive therapy.
- Additionally, we suggest screening for α3-AChR Ab autoantibodies in farmers with chronic moderate exposure of OP compounds, particularly in female farmers with history of pre-existing autoimmune disorders.

KEYWORDS
Acetylcholinesterase; Autoantibodies; Autoimmunity; Autoimmune gangliononeuropathy; Autonomic nervous system; Cardiac dysautonomia; Chronic organophosphorus (OP) poisoning; Insecticides; Farmers; Pesticides

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Address reprint requests and correspondence: Dr Dhanunjaya Lakkireddy, Overland Park Regional Medical Center, 12200 W 106th St, Overland Park, KS 66215. E-mail address: dlakkireddy@kchri.org.

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(PR interval: 114 ms, QT interval: 404 ms, QTc interval: 423 ms, and QRS duration: 84 ms). According to her Holter monitoring, the average heart rate (HR) was 64 beats per minute (bpm) with minimum HR 42 bpm and maximum HR 153 bpm. It also revealed 4 ventricular ectopic beats, 4 supraventricular ectopic beats, and 2148 bradycardia events. On head-up tilt table test, the orthostatic blood pressure changes were significant and there was a 30 mm Hg drop in systolic blood pressure from sitting to standing. Head-up tilt table test was also significant for orthostatic hypotension, with moderate increase in heart rate >30 bpm within 10 minutes of standing. Echocardiography was normal, without any abnormalities. During her initial visit, an implantable loop recorder for long-term monitoring of arrhythmias was inserted. Interrogation of implantable loop recorder at 3 months follow-up visit did not reveal any significant tachy-brady arrhythmias. After 3 months, the patient requested for its removal owing to discomfort and it was explanted. Holter monitoring showed intermittent bradycardia with positional change along with junctional rhythm. Heart rate variability was decreased with exercise and positional change. Gastric emptying test was abnormal, with delayed gastric emptying (moderate delay). Catecholamine blood test revealed increasing circulating levels of epinephrine and norepinephrine (arterial norepinephrine levels 0.38 ± 0.05 nmol/L [normal levels 0.07 ± 0.07 nmol/L] and arterial epinephrine levels 0.25 ± 0.05 nmol/L [normal levels 0.06 ± 0.17 nmol/L]). Sweat test was negative.

There was mild elevation of erythrocyte sedimentation rate and C-reactive protein. Twenty-four-hour urine measurements of norepinephrine and epinephrine were unremarkable. Electroencephalography, brain magnetic resonance imaging, and computerized tomography were negative and showed no other abnormal findings. Carotid Doppler imaging did not reveal any narrowing of carotid arteries. Nerve conduction studies confirmed peripheral neuropathy. No other central nervous system abnormalities were found. Complete blood count and basic metabolic profile (electrolytes and blood glucose) were within normal limits. Eventually, she was referred to Psychiatry and diagnosed with generalized anxiety disorder. She was prescribed selective serotonin reuptake inhibitor but she declined these medications.

The patient is a farmer by occupation for >30 years and her work routinely involves applying OP-containing pesticides to the crops. Although she wears personal protective

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**Figure 1** Clinical manifestations of varied exposure to organophosphates (OP): Summary of acute, intermediate, and chronic manifestations of OP poisoning. Chronic effects in farming populations exposed to harmful pesticides and insecticides can include well-established chronic OP-induced neuropsychiatric disorder (COPIND) syndrome and neurodegenerative diseases. Possible chronic sequelae can also include autoimmune-induced autonomic dysfunction, which might present in acute and chronic form. Autoimmune induced production of autoantibodies against alpha3 subunit of ganglionic acetylcholine receptors (α3-AChR) is speculative and needs to be confirmed in the future clinical studies.
equipment, she has had chronic inhalational exposure via direct spray during harvest season and direct contact with treated crops and soil. This prompted evaluation for toxic occupational exposure to OP. Indeed, we found elevated concentrations of OP metabolites in the urine (diphenyl phosphate [5.2 μg/g], 2,4-dichlorophenoxyacetic acid [0.73 μg/g], perchorlate [5.1 μg/g], 2-hydroxyisobutyric acid [5989 μg/g], N-acetyl-S-(-2-carbamoylthethyl) cysteine [20 μg/g], and 3-hydroxypropylmercapturic acid [244 μg/g]). Work-up for autonomic failure revealed the presence of autoantibodies against z3-AChR antibodies (78 pmol/L [normal range <53 pmol/L]). The patient initially declined immunosuppressive therapy but agreed to use fludrocortisone (0.1 mg daily), which resulted in some improvement of her symptoms.

**Discussion**

Dysfunction of the autonomic nervous system can be a manifestation of several underlying disorders, including but not limited to diabetes mellitus, degenerative disorders, congestive heart failure, storage disorders like amyloidosis, paraneoplastic syndromes, pharmacological effects, and autoimmunity. It is often under-diagnosed owing to vague symptoms and requires multidisciplinary effort. As dysautonomia can be a manifestation of underlying disease process (such as autoimmunity) that requires appropriate, disease-specific treatment, attempts should be made to look for the etiology while providing supportive care.

Autonomic and neuromuscular manifestations related to various types of OP exposure are depicted in Figure 1. The mechanism of autonomic failure, along with extrapyramidal symptoms, psychiatric symptoms, and neuropathy in chronic OP-induced neuropsychiatric disorder, is not well described in literature.3-7 The relationship between chronic exposure, acetylcholinesterase (AChE) inhibition, and symptoms is not well established either, but is postulated to be independent of AChE inhibition.4 Some studies suggest impaired axonal transport, oxidative stress, mitochondrial dysfunction, microglial activation, neuroinflammation, altered gene expression, and DNA damage in neuronal cells as the potential mechanisms. Physiologically, AChE has a neuromodulatory role in neuronal plasticity with associated long-term changes in synaptic efficacy. Thus, chronic suppression of AChE levels might result in long-term alteration of cognitive function following chronic exposure to OP pesticides.5 AChE level in this patient was 6408 IU/L (normal range 5300–10,000 IU/L).

In our clinical case, the patient was exposed to low levels of dermal and inhalational OP compounds over a long period of time. According to an isolated study, farmers who were chronically exposed to a mixture of pesticides including OP compounds developed autoantibodies against several cytoskeletal neural proteins, such as myelin basic protein.6 Antibodies in paraneoplastic syndrome have been reported to cause cell-mediated and often irreversible neuronal inflammation.3

To the best of our knowledge, we are the first to report antibodies against z3-AChR with concomitant autoimmune dysautonomia related to these z3-AChR autoantibodies. As patients who are seropositive for z3-AChR antibody might have underlying autoimmune disorder and accompanying dysautonomia, it is postulated that autoimmunity contributes to autonomic dysfunction. The z3-AChR antibodies are known to have specific predilection to AChR in the autonomic ganglia and were found in approximately 50% of cases of autoimmune autonomic ganglionopathy,9 with severity of symptoms correlating with higher titers. In another study, about 20% of the patients seropositive for z3-AChR antibodies had associated sensorimotor peripheral neuropathy or neuropsychiatric and extrapyramidal manifestations.10 In that study, up to 75% of patients with neurological manifestations responded to immunosuppressive therapy.10 Of note, as the alpha subunit is specific to the ganglionic receptor, there is minimal cross-reactivity between antibodies against ganglionic AChR and antibodies against the muscle AChR (which cause myasthenia gravis).3

**Conclusion**

We suggest the possibility of an autoimmune mechanism, specifically autoantibodies to ganglionic z3-AChR, in patients with dysautonomia or autonomic failure in the setting of chronic OP compound exposure.

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