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Inhaled Solvent Abuse Mimicking Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract

Exposure to n-hexane or toluene-containing solvents such as glue or gasoline can produce clinical symptoms and neurophysiological findings that can mimic chronic inflammatory demyelinating polyneuropathy. The authors present a case of a boy with severe sensorimotor polyneuropathy with demyelinating features. Cerebrospinal fluid testing and magnetic resonance imaging spine did not show findings typical of chronic inflammatory demyelinating polyneuropathy. His lack of response to immunosuppressive therapy prompted a nerve biopsy which was instrumental in confirming a diagnosis of chronic organic solvent exposure, subsequently confirmed on history. This case highlights the importance of additional testing to ensure diagnostic certainty which allows appropriate treatment and/or disease management to be tailored appropriately including in this instance, the involvement of mental health counseling and avoidance of immunosuppressant medication.

Keywords

inhalant abuse, peripheral nerve, n-hexane, solvents, chronic inflammatory demyelinating polyradiculoneuropathy

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The inhalation of volatile organic solvents can result from occupational exposure[1] or from their intentional inhalation for the purpose of achieving a euphoric or altered mental state. The abuse of inhaled solvents is more common among adolescents or young adults belonging to marginalized populations since these substances (ie, gasoline, spray paint, adhesive glue, and lacquer thinner) are legal, inexpensive, and relatively easy to obtain.[2,3]

Chronic inhalation of solvents, particularly those containing n-hexanes, n-butyl ketones, or tolulene,[4] can result in progressive and irreversible injury to the peripheral nervous system. Repeat exposure to lipophilic chemicals results in progressive demyelination and axonal loss.[5] Patients exhibit progressive weakness, sensory symptoms, decreased, or absent reflexes, consistent with a length-dependent polyneuropathy. Electrophysiological testing reveals a sensorimotor polyneuropathy with demyelinating features that can show variable involvement from one peripheral nerve to another.[6,7] Consistent with this are rare cases of patients with solvent inhalation abuse demonstrating focal conduction block[8] or multiple mononeuropathies[9] which can be confused with autoimmune neuropathies including acute or chronic inflammatory demyelinating polyradiculoneuropathy.[6]

We report a boy who presented with a chronic, insidious polyneuropathy. He met clinical and neurophysiological criteria for chronic inflammatory demyelinating polyradiculoneuropathy[10] but was subsequently determined that his presentation was a consequence of chronic inhalation of n-hexane.

Case Presentation

An 11-year-old boy presented with a history of distal weakness that had progressed over at least 3 months. Initial symptoms

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involved weakness and wasting of intrinsic hand and foot muscles. Weakness had progressed to involve his proximal muscles making ambulation difficult, and he has suffered a fall and a right ankle fracture just prior to hospitalization. He was cognitively normal. He had no oculobulbar weakness and no back pain or incontinence. He reported distal hypoesthesia in a stocking distribution but no dysesthesia or paresthesia. He initially reported no exposure to medication or toxins and denied the use of any drugs including inhaled solvents. Medical and family history was unremarkable. Physical examination noted normal cranial nerve examination but symmetric weakness (Medical Research Council Scale) as follows: deltoids 4+, flexor pollicis longus 3, hip flexors 4+, tibialis anterior 2, and extensor hallucis longus 1. He had upper limb hyporeflexia (1+) and lower limb areflexia. He had decreased pinprick sensation below his knees. Electrodiagnostic testing confirmed a severe sensorimotor polyneuropathy with demyelinating features (Table 1). He had absent sensory responses to bilateral median, ulnar, and sural nerves. Motor studies were abnormal to median, ulnar, peroneal, and tibial nerves, bilaterally with slowed conduction velocity (<50% lower limit of normal), prolonged latencies, and absent F-responses. Partial conduction block (50% amplitude drop) was apparent in his right ulnar nerve (between wrist and below elbow). Chronic inflammatory demyelinating polyradiculoneuropathy was suspected; however, clinical suspicion was raised when his cerebrospinal fluid protein and cell count were found to be normal, despite the severe demyelinating changes noted on nerve conduction studies. His magnetic resonance imaging brain and spine showed no evidence of nerve root thickening or enhancement seen. Intravenous immunoglobulin (IVIG) 2 g/kg was administered with no benefit. Prior to the administration of further immunosuppressant therapies, a sural nerve biopsy was performed. Semi-thin toluidine blue-stained sections of plastic embedded samples and ultrastructural study revealed enlarged axons with accumulation of neurofilaments and attenuated myelin sheaths (Figure 1). The absence of intermediate filaments in other cell types and osmiophilic condensation ruled out hereditary giant axonal neuropathy. There were no onion bulb formations and inflammatory infiltrate. The overall morphology suggested n-hexane exposure. In light of the biopsy findings, the boy subsequently disclosed his history of chronic inhalation of naphtha gas, a natural gas condensate that contains n-hexane.

Table 1. Nerve Conduction Studies Revealed Evidence of an Asymmetrical Sensorimotor Polyneuropathy With Demyelinating Features.[a,b]

	Right	Left	Normal
Motor			
Median nerve			
DML (milliseconds) wrist (to APB)	**4.2**		<4.2
CMAP (mV) wrist/elbow	**0.8/0.2**	NR	≥3.9
CV (m/s)	**37**		>47
Ulnar nerve			
DML (milliseconds); wrist (to ADM)	**5.2**	**6.2**	<3.4
CMAP (mV) wrist/b-elbow/a-elbow	**1.3/0.6[c]/0.6**	**0.7/0.1/0.3**	≥5.9
CV (m/s)	**8**	**23**	>47
Tibial nerve			
DML (milliseconds; ankle-AH)		**9.1**	<6.0
CMAP (mV) ankle/knee	NR	**0.6/0.5**	≥3.9
CV (m/s)		**35**	>39
Peroneal nerve			
DML (milliseconds; ankle-EDB)			<6.0
CMAP (mV)	NR	NR	≥2.4
CV (m/s)			>39
Sensory			
Median nerve			
PL (milliseconds; wrist-digit II)	**3.1**		<3.2
SNAP (μV)	**3.7**	NR	≥14
CV (m/s)	**37**		
Ulnar nerve			
PL (milliseconds; wrist-digit V)			<3.3
SNAP (μV)	NR	NR	≥9
CV (m/s)			
Sural nerve			
PL (milliseconds; calf-lat mall)			<4.2
SNAP (μV)	NR	NR	≥5
CV (m/s)			

Abbreviations: ADM, abductor digiti minimi; a-elbow, above elbow; AH, abductor hallicus; APB, abductor pollicus brevis; b-elbow, below elbow; CMAP, compound motor action potential; CV, conduction velocity; DML, distal onset motor latency; EDB, extensor digitorum brevis; NR, no response; PL, peak onset latency.

[a] Conduction block was noted in the right ulnar nerve, with a drop in amplitude of 50% between the distal (wrist) and more proximal (below-elbow) stimulation sites. F-responses were absent to the left ulnar and right median and tibial nerves (not shown). All sensory responses are antidromic.

[b] Bold values are abnormal.

[c] Conduction block between the distal (wrist) and more proximal (below-elbow) stimulation sites.

Discussion

Central and peripheral nerve myelin is comprised of up to 75% lipids, making it particularly sensitive to damage from lipophilic substances such as inhaled volatile solvents. Repeated clinical and electrophysiological testing has confirmed that demyelination can worsen even months after the last exposure has occurred, a phenomenon known as "coasting."[6–8,11]

Patients inhaling solvents for months or years have reported clinical decline that has ranged from acute (<1 month)[9] sometimes mistaken for Guillain-Barré syndrome,[12] to subacute (over 1-3 months),[6,7,13] to a chronic (>3 months) course.[8,11] It is unclear to what extent the rapidity of symptom onset is influenced by the quantity or frequency of inhalant exposure versus patient specific risk factors such as poor nutrition or exposure to other substances. In those with a slow, insidious onset of symptoms similar to that reported in our patient, solvent inhalation can closely mimic autoimmune polyneuropathies such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with clinical, electrophysiological, and even biochemical overlap noted between these 2

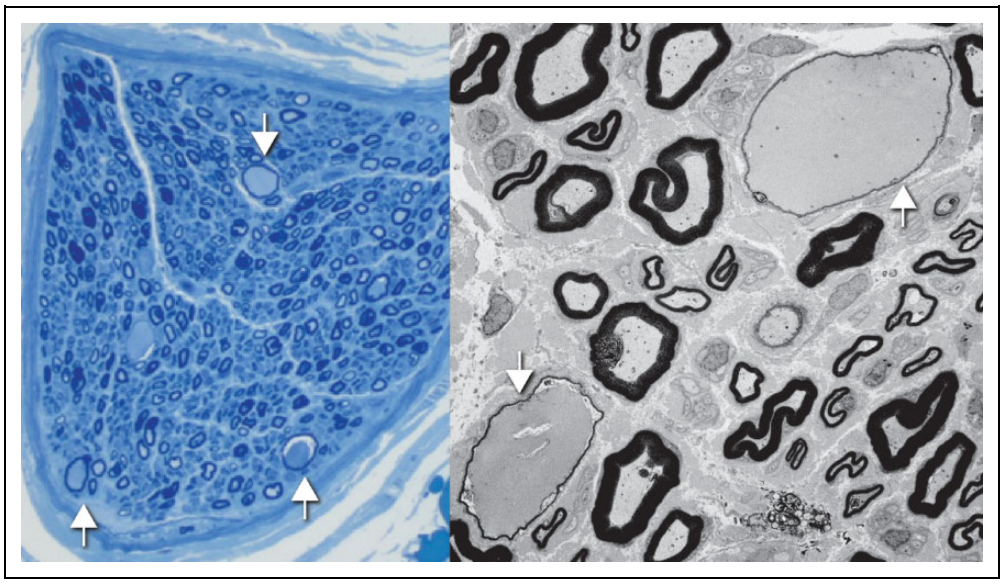

Figure 1. Sural nerve biopsy showing a semi-thin toluidine blue-stained sections (left; ×100) and ultrastructure (right; ×3870). Enlarged axons are seen (arrows) with attenuated myelin sheaths. The absence of intermediate filaments in other cell types, osmiophilic condensation, onion bulb formation, and inflammatory infiltrate suggested n-hexane exposure.

conditions. In cases where patients refuse to disclose a prior history of solvent abuse, this can present a significant diagnostic challenge. Patients with both conditions demonstrate chronic and insidious progression of distal weakness and sensory symptoms. Although most patients will report hypoesthesia or paresthesia, a smaller subset in both groups will report pain or dysesthesia.[14,15] Electrophysiological testing shows the greatest overlap and has the potential to lead to misdiagnosis if a history of solvent use is not obtained and/or if additional testing is not performed. Peripheral nerves in both disorders show patchy, segmental demyelination that can vary significantly from one nerve to another in the same patient. For patients with solvent inhalation, motor nerve conduction velocities have ranged from 16% to 91% of the lower limit of normal (Table 2). Temporal dispersion or conduction block, like that observed in our patient, is one of the electrodiagnostic criteria for CIDP,[10] but since this is a nonspecific electrodiagnostic finding that can be seen in a number of acquired and even hereditary neuropathies, other potential etiology must be considered. Cytoalbuminological dissociation, namely a mild elevation in cerebrospinal fluid protein with normal cerebrospinal fluid cell count, has been reported in 3 patients with inhaled solvent abuse.[6,8] Although cerebrospinal fluid protein is usually more commonly elevated and at higher levels in childhood CIDP where 87% to 100% of patients show cytoalbuminological dissociation,[16,17] the potential for overlap nevertheless exists. In cases where diagnostic uncertainty is present, a nerve biopsy can be particularly helpful at differentiating the two. This is particularly important in situations where the clinical or electrodiagnostic criteria for CIDP cannot be met or if biochemical (cerebrospinal fluid) or radiographic findings do not support the diagnosis. Clinical history is certainly paramount at assisting with clinical diagnosis, but in cases like this where the use of inhalant solvents is not initially forthcoming, biopsy can enable diagnostic clarity. Nerve biopsy and subsequent diagnostic clarity facilitated the access to addiction counselors and avoid the inappropriate use of immunosuppressant medications.

Patients with chronic solvent inhalation will show large or giant axons that are either devoid of myelin or lined by thin myelin sheaths (Figure 1). Myelin ovoids can also be seen in teased nerve fibers, although this procedure is no longer commonly performed. Unlike patients with CIDP, there will be no inflammatory infiltrates or onion bulb formations present on the nerve biopsy of inhaled solvent abuse patients.

The use of inhaled volatile solvents is indeed a worldwide problem. In 2018, the US National Survey on Drug Use and Health reported 9% of the US population aged 12 years and older to have used an inhalant at least once in their lifetime.[18] Studies have reported a higher rate of inhaled solvent abuse in some First Nations or Aboriginal communities, which is likely a reflection of the poor socioeconomic status where many First Nations' children live.[19]

In addition to its affect upon peripheral nerves, the central nervous system can also be affected particularly with chronic toluene exposure.[4] Magnetic resonance imaging of the brain in adolescents and young adults with chronic solvent abuse most commonly shows abnormal signal in the periventricular white matter and centrum semi ovale which can include other white matter tracts and later evidence of iron accumulation in deep gray structures.[20] Postmortem examination of individuals who have died of chronic inhalation of volatile solvents has revealed widespread demyelination of the central and peripheral nervous system, reduced number of oligodendroglia, axonal degeneration, and gliosis of ascending and descending long fiber tracts.[5] Acutely, cardiac arrhythmia is the most common cause of death due to solvent inhalation.[21,22]

Table 2. Characteristics of Patients With Inhaled Solvent Abuse Containing n-Hexane.

	Age, gender	Solvent	Clinical decline	CSF protein	Motor nerve conduction velocities (% LLN)
Current case	11-year-old M	Naphtha gas	Chronic (>3 months)	Normal	16% to 74% LLN; conduction block noted
King et al[6]	20- to 22-year-old M (N = 3)	Glue	Subacute (4 weeks) to chronic (>2 years)[a]	High (in 2/3)	34% to 80% LLN; 1 patient diagnosed with CIDP, treated with corticosteroids × 2 months (no response)
Goto et al[7]	18- to 25-year-old F (N = 3) and 22-year-old M	Adhesive	Subacute (1-2.5 months)[a]	Normal (2)	58% to 78% LLN
Smith[8]	25-year-old M	Rubber cement	Chronic[a]	High	34-76% LLN
Burns et al[9]	14-year-old F	Gasoline	Acute (3 weeks)	Normal	83% to 91% LLN; mononeuritis multiplex (focal right median neuropathy) superimposed on a mild sensorimotor polyneuropathy
Oh[11]	20-year-old M	Lacquer thinner	Chronic (months)[a]	Normal	43% to 66% LLN
Prockop[12]	17- to 22-year-old M (N = 7)	Lacquer thinner	Not specified [b]	Normal	<55% LLN
Korobkin[13]	29-year-old M	Contact cement	Subacute (2.5 months)	Normal	55% to 80% LLN
Summary	11- to 29-year-old 15 M; 4 F			High 3/19, 16% patients	16% to 91% LLN

Abbreviations: CSF, cerebrospinal fluid; F, female; M, male; LLN, lower limit of normal.
[a]Progressive clinical and/or electrographic deterioration ("coasting") for weeks-to-months after stopping inhalation.
[b]Two of 7 patients initially diagnosed with Guillain- Barré syndrome implying acute symptom onset.

In our current age of increasing access to rapid genetic testing, nerve biopsy is rarely performed. However, in suspected acquired demyelinating polyneuropathies such as this, where diagnostic uncertainty exists, a nerve biopsy can provide important clues to and avoid the unnecessary use of immunosuppressant medications.

Author Contributions

ST drafted the manuscript, contributed to conception and design of the case report, contributed to acquisition, analysis, and interpretation of clinical data, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. JM contributed to acquisition, analysis, and interpretation of all neuropathological test results, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. AD contributed to acquisition of clinical data, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. HJM drafted the manuscript, contributed to conception and design of the case report, contributed to acquisition, analysis, and interpretation of all clinical and neurophysiological (NCS/EMG) test results, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical Approval

Research ethics board approval is not required for a single case report at our institution.

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