Thinking Beyond Guillain–Barré Syndrome: Acute "Demyelinating" Neuropathy with Myoclonic Encephalopathy after Arsenic Trioxide Therapy

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Abstract

In addition to its well-recognized roles as a poison and as a component of traditional medications, arsenic has recently reentered the modern therapeutic armamentarium for the treatment of hematological neoplasms. The narrow therapeutic index of arsenic trioxide (ATO) may lead to significant neurologic toxicity.

Methods We report the occurrence of myoclonus, encephalopathy, and a multifocal neuropathy with a demyelinating pattern on electrophysiological testing in an 82-year-old man with acute promyelocytic leukemia, who received ATO therapy in accordance with published protocols. We systematically review previous reports of demyelinating polyneuropathy attributed to arsenic intoxication and discuss the likely pathogenesis of peripheral nerve dysfunction in this setting.

Discussion This pattern of peripheral nerve dysfunction contrasts with but tends to evolve into the chronic sensorimotor axonal type more commonly associated with arsenic intoxication. Electrophysiological findings and elevated cerebrospinal fluid protein levels have, in the past, led to this relatively rare entity being confused with Guillain–Barré syndrome leading to a significant delay in reaching the correct diagnosis and instituting appropriate treatment. The presence of encephalopathy or other organ system dysfunction and identification of potential arsenic exposure are important clues to investigate for possible intoxication. Electrophysiological findings in acute arsenic neuropathy follow a predictable course over weeks, ultimately resembling the more common chronic sensorimotor axonal form.

Keywords
- arsenic trioxide
- neuropathy
- demyelinating
- myoclonus

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Introduction

Widely acknowledged as a poison and administered with both suicidal and homicidal intent, arsenic has had a checkered history as a therapeutic agent through the ages. From Hippocrates and Galen to more recent use as neoarsphenamine, melarsoprol, or Fowler's solution (1% arsenic trioxide [ATO]), organic or inorganic arsenic had been employed in the treatment of syphilis, yaws, and trypanosomiasis as solutions, tablets, pastes, and injections. It continues to be used as a pesticide and in Chinese and Indian traditional medicine and some homoeopathic remedies. In addition, chronic low-level exposure through groundwater remains a serious public health issue is many areas.[1,2] Arsenic has reentered the modern therapeutic armamentarium as ATO, widely used in the treatment of acute promyelocytic leukemia (APL) and potentially in multiple myeloma and other hematologic malignancies and solid tumors based on its mechanism as an inducer of apoptosis via release of a mitochondrial flavoprotein apoptosis-inducing factor. When combined with all-*trans* retinoic acid (ATRA), ATO is now the standard of care in treating APL.[1,3–7]

While acute arsenic intoxication is often lethal within days due to bloody diarrhea, cardiomyopathy, pancytopenia, disseminated intravascular coagulation, or acute renal injury, survival beyond 3 weeks permits the appearance of neurological symptoms including a confusional state, seizures, or peripheral neuropathy.[8,9] Distal symmetric chronic axonal sensorimotor polyneuropathy is the most frequent and best-recognized neurological complication of arsenic intoxication, usually developing insidiously after chronic low-level exposure.[1,2,10–21] Systemic manifestations of the toxidrome may be minimal in this setting, necessitating a high level of suspicion to arrive at the correct diagnosis, although the characteristic teardrop skin pigmentation and Mees' lines on the nails are important clues.[1,2,9,20] Less well-known is the development of acute or subacute polyneuropathy that may develop within days of massive intoxication in association with gastrointestinal, cardiovascular, hematologic, or encephalopathic symptoms.[1,8–10,15,16,21,22] In contrast to the symmetric, axonal sensorimotor polyneuropathy typically associated with arsenic intoxication, an acute or subacute demyelinating polyneuropathy beginning a few weeks after arsenic exposure has been described much less frequently and may be mistaken for Guillain–Barré syndrome (GBS).[8,9,13,16,17,19,21–29] Patients demonstrate electrophysiological features consistent with demyelination, including slowing of motor nerve conduction velocity (NCV), prolonged distal latencies, partial conduction blocks, or abnormal F-wave studies.[8,9,11,13,14,16,17,19–31] The dose of arsenic and the duration of exposure may influence the type of neuropathy that may result—whether axonal or demyelinating.[1,8,9,19,28]

We report a patient with APL who developed an acute polyneuropathy with demyelinating characteristics on electrophysiological testing in the setting of myoclonic encephalopathy after ATO and ATRA treatment. Previous reports of demyelinating polyneuropathy attributed to arsenic intoxication are reviewed, and we discuss the likely pathogenesis of peripheral nerve dysfunction in this setting.

Case Report

An 82-year-old man with rheumatoid arthritis and psoriasis (both currently inactive following treatment), hypertension, previous renal vein thrombosis, thoracic herpes zoster and nephrotic syndrome 2 years prior—attributed to gold therapy and now in spontaneous remission—was evaluated for worsening pancytopenia and in February 2022 was diagnosed with APL. Quantitative real-time polymerase chain reaction (PCR) detected the PML-RARA t(15;17) translocation and subsequent chromosome analysis of cultured interphase cells from bone marrow aspirate revealed a gain of chromosome 8 and a translocation between the long arms of chromosome 15 and 17 in 40% of cells examined. Fluorescence in situ hybridization analysis detected a PML::RARA [t(15;17)(q24;q21)] gene rearrangement in approximately 70% of cells examined. He was commenced on ATRA 40 mg twice a day and 5 days later on concomitant ATO, infusions of which were complicated by hypotension, orthostatic dizziness, and possible differentiation syndrome. Three days after commencing ATO and again 3 weeks later he had bouts of epistaxis managed conservatively. Pedal edema gradually worsened during this time. A dermatology consult for skin rash on day 25 of ATO therapy returned a diagnosis of xerosis of the skin, eyes, and nose secondary to ATRA with acute herpes simplex virus infection over the right buttock.

On day 6 of ATO treatment jerky involuntary limb movements and lip smacking were noted intermittently. At that time, he was noted to have absent ankle jerks and sluggish knee jerks with reduced distal pinprick perception to midshin bilaterally. Perception of vibration was normal and there was no motor weakness. He was noted to be intermittently somnolent and lethargic on day 16 but subsequently improved. ATO therapy was continued for 26 days, with a cumulative total dose of 249 mg. After the 26th dose, he became febrile, drowsy, and disoriented and had a generalized seizure followed by ongoing arrhythmic jerking of the limbs with nearly continuous facial grimacing movements. Antiseizure therapy with levetiracetam was initiated and ATO and ATRA were withheld. At evaluation the next day, ongoing myoclonic jerking of the upper limbs and facial choreiform movements were noted. There was relative paucity of lower limb movements. He remained very drowsy but responded appropriately to painful stimuli.

An electroencephalogram (EEG) demonstrated slowing of background activity consistent with diffuse cerebral dysfunction, and no periodic complexes or epileptiform discharges were seen. Contrast-enhanced magnetic resonance imaging of the brain was unremarkable. Cerebrospinal fluid (CSF) protein and glucose levels were normal, without pleocytosis and with negative multiplex viral PCR and cryptococcal antigen test. CSF arsenic levels were 130 nmol/L (10 µg/L) 36 hours after the last dose of ATO. A spot urinary arsenic collected 5 days later was elevated at 11.95 µmol/L (895 µg/L, reference range < 35 µg/L or < 0.47 µmol/L) with urinary

creatinine at 4.1 mmol/L. Twenty-four-hour excretion of arsenic was measured at 8.60 µmol/day (reference range 0.5–2.0) and of creatinine at 6 mmol/day (estimated glomerular filtration rate 42 mL/min/1.73 m^2).

After cessation of ATO, we initiated chelation therapy with meso-2,3-dimercaptosuccinic acid (DMSA, Succimer) for 9 days followed by 2,3-dimercapto-1-propanesulphonic acid sodium (DMPS) for 5 days. Twelve days after ATO cessation weakness of the proximal upper limb muscles and global flaccid lower limb weakness were obvious, with absent knee and ankle jerks. Reflexes remained normal in the upper limbs. Perception of pain—as evidenced by grimacing—was preserved in the upper limbs. Electrodiagnostic testing demonstrated normal right ulnar sensory amplitudes, low-amplitude right sural sensory responses, with normal sensory NCV. Motor amplitudes and NCV and F-waves from the right ulnar nerve were normal, while the peroneal and tibial nerves demonstrated normal motor responses on distal stimulation with a complete conduction block on proximal stimulation, and absent F-waves. Electromyography (EMG) was normal in the right biceps brachii, while markedly reduced recruitment was noted in the right vastus lateralis, gastrocnemius, and tibialis anterior. Motor unit action potential morphology was normal in all muscles, and occasional fibrillations were seen in the tibialis anterior. The study was consistent with a motor demyelinating neuropathy in the lower limb.

Gradual improvement in encephalopathy and limb power continued, although a severe bilateral foot drop and loss of ankle jerks persisted. Six weeks after ATO cessation he was alert and oriented with a fine hand tremor, mild and intermittent limb myoclonus, involuntary grimacing of face, and choreiform hand movements with severe distal lower limb weakness, wasting, and hypoalgesia. At further review 4 months later, he was able to ambulate with a 4-wheeled walker or a single-point cane, using bilateral ankle-foot orthoses. Bone marrow examination after recovery from the acute illness demonstrated cytogenetic remission, and ATRA was recommenced for four cycles as monotherapy. Ten months after the original diagnosis methotrexate and 6-mercaptopurine were added to the treatment regimen for APL.

Discussion

Neurologic Complications of ATO Therapy

APL is a life-threatening neoplasm, representing a subset of acute myeloid leukemia with a characteristic reciprocal t (15;17)(q22;q21) chromosomal translocation generating the *PML-RARA* fusion gene [4r1]. The treatment of APL with ATO and ATRA leads to high cure rates but has rarely been complicated by encephalopathic symptoms and myoclonus. The narrow therapeutic index of ATO mandates close monitoring during treatment: inorganic arsenic is lethal at doses exceeding 1 to 3 mg/kg (as a bolus) or 0.6 mg/kg/day over 14 days.[1,7] However, encephalopathic symptoms have been observed to follow acute exposure to significantly lower doses of arsenic: similar to our patient, Rhee et al reported acute myoclonus beginning on day 6 of treatment with ATO, associated with slowing of EEG background rhythms and frequent triphasic jerks consistent with a toxic-metabolic etiology. Myoclonus resolved after withholding treatment, and did not recur after ATRA was restarted in combination with idarubicin.[6] A profound agitated delirium with myoclonus and tremor followed attempted suicide with 54 g of ATO.[32] Nonspecific encephalopathic symptoms including neurocognitive changes have been reported after exposure to ATO[33] as well as to other forms of arsenic, reported in 5 to 9% of cases,[34,35] and "reactive" encephalopathy is a frequent complication of treatment of trypanosomiasis with organic arsenicals such as melarsoprol, occurring in up to 10% of these patients, and historically with arsphenamine treatment of syphilis.[14,36,37] Interestingly, this idiosyncratic reaction to melarsoprol usually manifesting as acute hemorrhagic leukoencephalitis with brainstem involvement is thought to be immunologically mediated, with certain major histocompatibility complex class I haplotypes conferring 6.5-fold risk.[36,38] In addition to ATO, myoclonus and other movement disorders (tremors, ataxia, and nystagmus) have been reported after exposure to potable water contaminated with diphenylarsinic acid in Kamisu, Japan, occurring up to 10 years after exposure began.[39]

Encephalopathy is likely due to a direct toxic effect of arsenic on the brain, but definite dose–response relationships have not been defined. Arsenic crosses the blood–brain barrier and enters CSF during treatment with oral ATO, with concentrations reportedly ranging from 3.5 to 318.9 nmol/L (median, 95.8 nmol/L),[40–42] similar to those found in our patient 36 hours after the last dose of ATO. It is conceivable that substantially higher CSF levels were achieved during treatment. CSF arsenic levels maintain a linear relationship to plasma concentrations at 17.7% the plasma level.[40] Autopsy data have confirmed the accumulation of arsenic in brain and spinal cord tissue after oral treatment with melarsoprol.[32] Established hemorrhagic infarction has been demonstrated in fatal cases with multiple areas of microcavitary necrosis, microglial proliferation, foci of perivascular red cells, and histiocytes with extravasation of blood into white matter.[37] Chronic exposure to diphenylarsinic acid was associated with reduced blood flow and glucose metabolism in the cerebellum, brainstem, and temporal and occipital lobes.[39]

Peripheral neuropathy is a rare side effect of ATO therapy, having been reported in only 1 of 255 patients in various studies,[7] but in 18 of 34 patients in another, possibly related to higher ATO doses administered (cumulatively 12.75 mg/kg over 85 doses). Severe neuropathy is rare, affecting only 0.5% of patients, usually of the sensorimotor axonal type.[2,7,43–46] Our patient is similar to the report by Kühn et al, which describes diffuse encephalopathy, hypernatremia, and a severe symmetric sensorimotor axonal neuropathy after ATO therapy. Partial recovery of nerve function followed cessation of ATO treatment, but severe distal weakness persisted in all limbs after 6 months.[43] While our patient did have autoimmune conditions that may be associated with neuropathy, these were inactive following treatment.

The temporal relationship of the neuropathy with ATO therapy and encephalopathy, its partial improvement after chelation, and typical clinical and electrophysiological features similar to other, previously reported cases of large-fiber neuropathy following arsenic intoxication all support our diagnosis of a toxic neuropathy consequent to ATO exposure.

Arsenic-Related "Demyelinating" Neuropathy

We reviewed available reports of demyelinating neuropathy attributed to arsenic toxicity, by searching PubMed, EMBASE, Google, and Google Scholar databases using the keywords "arsenic" and "demyelinating" and "neuropathy" to identify all published reports on patients diagnosed with a multifocal demyelinating neuropathy on nerve conduction study (NCS)/EMG by a neurologist attributed to arsenic exposure. The last search was performed on April 18, 2024. Reports describing slowing of motor NCV in isolation—as is commonly seen with the more typical chronic axonal sensorimotor form of arsenic neuropathy—were excluded. Clinical details of 19 patients are summarized in ►**Table 1**.

Three female patients and 15 males were included, aged between 9 and 82 years. One patient's sex was not specified. The onset of neurological symptoms generally occurred between 1 week and 38 days after exposure to arsenic, although in one patient with chronic inflammatory demyelinating polyneuropathy (CIDP), neuropathic symptoms had been present for 2 years and had been attributed to chronic arsenic intoxication from ground water.[25] Other sources of arsenic included therapeutic administration (ATO in the current case, melarsoprol,[14] and indigenous medicines[13,16,17,23]), a contaminated concoction of opium,[28] occupational exposure,[26] homicide,[9,21] and suicidal[8,29] or accidental[29] ingestion. The mode of poisoning was not defined in five patients. Reported levels of arsenic in body fluids or tissues varied widely, with levels ranging from 1.5 times the upper limit of normal (ULN) in urine to 700 times the ULN, and 2 to 475 times the ULN in hair and nails. One autopsy study[14] reported very high levels of arsenic in spinal cord tissue, less marked elevations in the brain, and undetectable to low levels in the peripheral nerves in a patient with multifocal demyelinating neuropathy without clinical evidence of encephalopathy.

Reported neuropathic symptoms included limb weakness and sensory loss, often progressing proximally from the distal extremities, areflexia, and painful distal paraesthesia. Sensory ataxia was a feature in six patients, but it is likely that severe weakness precluded its detection in others. Pain (either paraesthesia or myalgia) was reported as a significant symptom in 12 patients. Four patients developed respiratory failure due to neuromuscular weakness, but only one had bulbar and facial muscle dysfunction. Apart from our patient with confusion, myoclonus, and chorea, five patients demonstrated encephalopathic symptoms ranging from headache to confusion, memory difficulties, behavior change, and frank delirium. The systemic arsenic toxidrome included gastrointestinal, dermatologic, hematologic, renal, hepatic, and cardiovascular dysfunction. Only two patients in this

Table 1 Previous reports of patients with arsenic-related multifocal demyelinating neuropathy

Serial no.	Ref	Year	Age/Sex	Time to onset of neurological symptoms	Source of intoxication	Arsenic levels (reference range)	Neuropathic features	Encephalopathy	Systemic features	Treatment	Course
1	Current	2023	82/M	26 d	ATO for APL	CSF 0.13 µmol/L (10 µg/L), spot urinary 11.95 µmol/L (895 µg/L, reference range < 35 µg/L or < 0.47 µmol/L. 24-h urinary arsenic 8.60 µmol/day (0.5–2.0)	Severe lower limb areflexic weakness, bilateral foot drop, distal sensory loss	Yes, with myoclonus and chorea	Pedal edema, hypotension	DMSA, DMPS	Gradual improvement in encephalopathy and involuntary movements over weeks, persistent distal weakness, sensory loss, and wasting
2	13	2019	9/F	3 wk	Indigenous medicine for obesity	Blood 29.3 µg/L (0.4–11); urine 323 µg/L (< 35)	Progressive distal numbness and weakness, areflexia		Acute diarrhea at onset, Mees' lines	Antioxidants, vitamins physiotherapy	Upper limb deficits resolved by 18 months
3	26	2018	26	Unclear, possibly acute	Occupational exposure to arsine gas	Urine 715.0 µg/L, blood 95 µg/L	Pain paraesthesia, dysesthesia, and weakness of lower limbs	Memory loss, vertigo	Respiratory and gastrointestinal complaints, liver dysfunction		
4	16	2016	40/M	4 wk	Indigenous medication for respiratory infection	24-h urine 405.2 µg/L	Numbness, painful paraesthesia in distal limbs progressing proximally, sensory ataxia, areflexia, distal weakness		Desquamating skin rash, raindrop pigmentation, Mees' lines	Analgesia	Subsided in 6 weeks

Table 1 (*Continued*)

Serial no.	Ref	Year	Age/Sex	Time to onset of neurological symptoms	Source of intoxication	Arsenic levels (reference range)	Neuropathic features	Encephalopathy	Systemic features	Treatment	Course
							progressing to profound quadriplegia				
5	17	2013	51/M	3 wk	Herbal patch for anal fistula	Urine arsenic 541 µg/g creatinine (normal: < 100). Mercury level of 5.8 µg/L (normal: < 5 µg/L)	Numbness and progressive weakness of extremities, severe weakness, and wasting of lower limbs		Fever, anal pain + perianal gangrene, dizziness, pruritic rash, anorexia, normocytic anemia	Plasma exchange, subsequent DMPS	Increased arsenic and mercury urinary excretion after DMPS. Systemic features resolved, persistent neuropathic deficits
6	19	2012	43/M	Symptoms evolved over 25 days		Urine 240.7–507.9 µg/L	Bilateral proximal limb weakness and distal paresthesia, areflexia in legs			IVIg 2 g/kg over 5 days	Improved muscle strength
7	8	2005	50/M	9 d	Suicidal ingestion	Urine 8000 µg/L (< 40)	Paraesthesia, numbness, and weakness of distal limbs, areflexia, sensory ataxia	Behavior change, disorientation, obsessiveness, persecutory delusions	Acute diarrhea and vomiting, skin rash, renal failure, transaminitis, rhabdomyolysis	BAL	Rash and behavioral symptoms resolved in days, slow improvement in neurological function over 9 months
8	21	2004	55/M	2 mo	Possible homicide	Urine 6171–6229 µg/g creatinine (< 50), hair 13.2–17.1 µg/g (< 1)	Bilateral distal limb weakness paresthesia, numbness, areflexia, sensory ataxia	Disorientation, delirium, visual hallucinations	Nausea, vomiting, abdominal pain, dizziness, hypotension, tachycardia, pancytopenia, rash	BAL	Worsening, respiratory failure, death
9	23	1996	34/F		Possibly traditional medicine	Urine 3176 µg/L (< 80)	Distal burning, numbness, and weakness, sensory ataxia, areflexia; subsequent worsening with increased pain, facial/bulbar weakness, and flaccid quadriplegia with respiratory failure	Headache	Vomiting, wheezing, arrhythmia, syncope, pancytopenia	IVIg 0.4 g/kg/day for 5 days reduced pain, limb strength and vital capacity transiently, succimer	Improved after 6 weeks, residual severe distal limb weakness
10	28	1991	35/M	6 wk	Contaminated opiate concoction	Urine 73.1 µg/g creatinine (normal: < 9), nails 7.1 µg/g (1.5–3)	Progressive ascending distal limb weakness, distal numbness, sensory ataxia, areflexia, respiratory failure		Fever, vomiting, diarrhea, Mees' lines	D-penicillamine	Improved respiratory and limb function, "almost independent" for daily activities at 3 months
11	14	1990	24/F	38 days after treatment	Melarsoprol for trypanosomiasis	232 ng/g dry tissue brain 2030 spinal cord, < 3 distal nerves	Myalgia, distal paraesthesia + hyperesthesia, flaccid quadriparesis, areflexia, tachycardia attributed to dysautonomia	No	Renal failure (acute tubular necrosis), transaminitis, heart failure		Death
12	25	1989	63/M	2 y	Well water	Hair 311.49 mg/g	Distal sensory loss and sensory ataxia, mild distal weakness, areflexia, tremor	No	No	Prednisone, plasma exchange	Responded to immunotherapy, relapse on steroid withdrawal

(*Continued*)

Table 1 (*Continued*)

Serial no.	Ref	Year	Age/Sex	Time to onset of neurological symptoms	Source of intoxication	Arsenic levels (reference range)	Neuropathic features	Encephalopathy	Systemic features	Treatment	Course
13	9	1986	61/M	Symptoms evolved over 1 week		Hair 2895 μg/g (< 65)	Distal paraesthesia, numbness, and ascending weakness, areflexia		Acute vomiting and diarrhea, anemia, leukopenia, transaminitis, renal failure, pleural effusions, skin desquamation		Stabilized 6 weeks following onset of gastrointestinal symptoms
14	9	1986	63/M	Symptoms evolved over 2 weeks		Urine: 35,000 ppb (< 50), nail 8.6 μg/g (< 0.36), hair 160 ppm (< 0.5)	Distal wasting and weakness, areflexia, distal extremity dysesthesia, and numbness evolving to flaccid areflexic quadriplegia with respiratory failure	Headache, confusion	Transaminitis, renal insufficiency, pancytopenia, congestive heart failure, and a skin rash	BAL	Cognition and rash improved in a week. Remained quadriplegic for months
15	9	1986	62/M	3 wk	Homicidal poisoning	24-h urine 76 μg/L (< 50), hair 4.2 μg/g (< 1.9)	Distal paraesthesia, numbness, and ascending weakness, areflexia		Shortness of breath, nausea, vomiting, diarrhea, malaise, myalgia, arthralgia		Improved with rehabilitation
16	9	1986	31/M	Symptoms evolved over 9 days		24-h urine 1,500 μg/L (< 50)	Distal paraesthesia, numbness, and ascending weakness, evolving to flaccid areflexic quadriplegia with respiratory failure		Nausea, vomiting, and diarrhea, tachycardia, pancytopenia, transaminitis, skin desquamation, Mees' lines	Plasma exchange, penicillamine	
17	22	1982	21/M	Unclear, possibly subacute		Normal in urine, hair 31 μg/g (< 0.5)	Distal paraesthesia and numbness, areflexia, severe distal weakness, and sensory loss with foot drop		Skin thickening over palms and soles, erythematous and macular rash, anemia		
18	29	1977	56/M	2 wk	Accidental	Urine 0.25 mg/L (< 0.1)			Acute vomiting, diarrhea	BAL	Persistent deficits at 5 years
19	29	1977	46/M	10 d	Suicidal	Urine 2 mg/L (< 0.1)	Numbness, initially distal, rapidly followed by severe distal weakness, areflexia, large-fiber sensation loss distally		Hypotension, tachycardia, acute kidney injury, rash	BAL	Improved after 9 months. Persistent deficits at 8 years: distal wasting and weakness

Abbreviations: ATO, arsenic trioxide; APL, acute promyelocytic leukemia; BAL, British Anti-Lewisite; CSF, cerebrospinal fluid; DMPS, 2,3-dimercapto-1-propanesulphonic acid; DMSA, meso-2,3-dimercaptosuccinic acid; F, female; IVIg, intravenous immunoglobulin; M, male.

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cohort had no systemic symptoms: the patient with CIDP alluded to above[25] and another with acute acquired demyelinating polyradiculopathy evolving over 25 days and responding to intravenous immunoglobulin therapy.[19]

Nerve conduction studies demonstrated characteristics of a demyelinating neuropathy in all patients with available data (►**Supplementary Table S1**, online only). Conduction blocks or temporal dispersion were noted in 13 patients and F-waves were reported to be abnormal (absent or with prolonged minimum latencies) in 7. Electrophysiological changes relatively spared the ulnar nerves over the median and/or radial in four patients and the tibial over the peroneal nerves in one, and were generally more marked in the lower limbs than the upper. Serial NCS evaluations in eight patients revealed progressive worsening of the neuropathy over weeks with loss of sensory and subsequently motor responses and EMG evidence of denervation. The early features indistinguishable from a segmental demyelinating polyradiculoneuropathy evolve over weeks into features commonly reported in the distal chronic sensorimotor axonal form of arsenic neuropathy[9,29] with motor NCV reaching its nadir around 3 months after exposure. Repeated electrophysiological testing 1 to 8 years after arsenic exposure showed some improvement, often in upper limb motor NCV, but with severe persisting abnormalities in the lower limbs and in sensory nerves. In keeping with this pattern of evolution, NCS findings were normal in one patient at day 17 of hospital admission,[8] demonstrated an acquired demyelinating neuropathy at day 33, and worsening at day 62 with denervation on EMG. Ten months later motor NCS were normal in the upper limbs, without recovery of sensory responses. The cohort of patients with arsenic neuropathy studied by Oh had similar findings, with marked abnormalities in sensory and F-wave studies, low motor amplitudes, and slowed motor NCS particularly in lower limb nerves. Conduction block was reported in 4 of 13 patients and temporal dispersion in 2. Serial NCS confirmed progression of abnormalities, with appearance of conduction blocks followed by a severe axonal pattern.[20] The dissociation between sensory and motor nerve involvement might reflect preferential involvement of sensory nerve fibers over motor.[20] CSF protein was elevated in 4 of 10 patients in Oh's cohort, while CSF was normal in four patients in our review, with nine demonstrating "albuminocytologic dissociation." One patient with trypanosomiasis had a cellular CSF with elevated protein.[14]

Many of the patients in ►**Table 1** were initially thought to have GBS, not unexpectedly in view of the clinical syndrome of acutely evolving lower motor neuron weakness with areflexia, NCS suggesting demyelination, and in some cases elevated CSF protein suggesting "albuminocytologic dissociation."[19,20,23] Based on the presumption of an inflammatory demyelinating neuropathy five patients had received intravenous immunoglobulin or plasma exchange. Like our patient, that of Berbel-García et al had a "demyelinating" polyneuropathy but with later development of encephalopathy that prompted reconsideration of the diagnosis and subsequent identification of arsenic intoxication.[21] As pointed out by Feit et al, albuminocytologic dissociation can be seen in toxic neuropathies and vasculitis among other conditions, does not confirm a diagnosis of GBS, and should not diminish enthusiasm for further investigations into the etiology of the neuropathy.[22] The presence of encephalopathic symptoms (in 6 of 19 patients in this series) and more importantly, systemic involvement (in all but two patients) and identification of potential arsenic exposure serve to discriminate arsenic-related acute neuropathy from GBS. Greenberg[23] suggested that motor NCV slowing in proximal arm segments with normal velocities and distal latencies for other motor segments, as seen in his patient with arsenic neuropathy, would be an unusual feature for GBS. Goddard et al used the proximal F-loop latency (M-wave latency at the wrist + F-wave latency at the wrist – 2× M-wave latency at the axilla) to discriminate arsenic neuropathy from GBS.[24] The patient with CIDP reported by Costigan and Krendel[25] did have elevated tissue arsenic concentrations, but no acute exposure was identified and urinary arsenic levels did not rise after chelation with dimercaprol. While his neuropathy was attributed to chronic arsenic poisoning from ground water in the absence of systemic manifestations of arsenic intoxication, he responded to immunomodulatory treatment as usually employed in the treatment of typical CIDP. There have been no other reports of a CIDP-like illness associated with arsenic intoxication, and the link between arsenic and this patient's neuropathy remains somewhat speculative. In contrast, a man with progressive acute quadriparesis beginning 20 days after commencing a course of herbal medicine was reported by Kim et al.[19] He had no systemic features to suggest arsenic intoxication but did have elevated urinary levels of arsenic that fell over 10 days after cessation of the herbal preparation suggesting a possible temporal relationship of acute arsenic intoxication to his neuropathy. Interestingly, he was reported to improve after treatment with intravenous immunoglobulin. A causal relationship between the likely acute exposure to arsenic and the development of his demyelinating immune-mediated neuropathy in the absence of other organ system dysfunction remains to be determined.

Once arsenic intoxication was identified as the cause, treatment involved removal of the patient from the source of exposure, and chelating agents were employed in nine patients. After an often-stormy initial course requiring significant supportive measures for systemic involvement and neuromuscular respiratory failure, gradual improvement in peripheral nerve function became apparent over weeks to months. Two patients died during the acute illness. In the rest, systemic symptoms and encephalopathy improved relatively quickly but 9 of 11 patients with long-term follow-up (6 weeks–8 years) had persistent neuropathic deficits, often severe and predominantly affecting the lower limbs to a greater degree. In a large series of 40 patients, only 6 recovered completely within 40 days to 6 years.[12]

The role of chelating agents in the treatment of arsenic poisoning is uncertain. Dimercaprol and penicillamine are reportedly effective in controlling the systemic effects of arsenic poisoning including the development of neuropathy when given within hours of exposure, but are clearly ineffective once neuropathy is established.[2,11,47] DMPS has been employed in patients whose systemic toxidrome progressed

despite treatment with DMSA or dimercaprol,[27,48] and may protect against the development of arsenic-related neuropathy.[49]

Peripheral Nerve Dysfunction Due to Arsenic

Nerve biopsy was performed in three patients in our series. One demonstrated features typical of CIDP, and the authors attributed the patient's chronic demyelinating neuropathy to arsenic exposure via well water.[22] Severe axonal and myelin degeneration was noted in another patient[9] while one of Le Quesne and McLeod's patients showed a severe axonal process with reduced large fiber density and myelin ovoids without evidence of segmental demyelination or remyelination.[29] In general, histological examinations of peripheral nerves from patients with arsenic poisoning demonstrate axonal degeneration, predominantly affecting the large myelinated fibers, correlating with EMG evidence of axon loss and muscle denervation.[29,31] Nine of the patients reported by Oh had sural nerve biopsies, demonstrating reduction of myelinated fibers and active axonal degeneration, but segmental demyelination was not observed.[20] Chhuttani and Chopra,[15] in contrast, suggested that segmental demyelination and axonal degeneration might be equally prominent pathological features of the neuropathy produced by arsenic, from their observation of demyelination and remyelination in teased fiber preparations. This segmental demyelination may represent a secondary phenomenon, akin to that seen in other neuropathies, and may provide a possible mechanism for the slowing of nerve conduction.[30] Alternatively, the "demyelinating" features noted on NCS may arise from large myelinated fiber loss, with conduction being restricted to smaller diameter regenerating nerve fibers.[30] One patient with trypanosomiasis and melarsoprol-induced multifocal neuropathy had loss of large myelinated fibers and Wallerian degeneration with myelin balls in intramuscular nerve twigs at autopsy. The extremely high concentration of arsenic in the spinal cord with minimal amounts in peripheral nerves and the presence of anterior horn cell vacuolation and degeneration with axoplasmic neurofilamentous masses led the authors to hypothesize that arsenic induces a toxic neuronopathy with subsequent peripheral nerve damage manifested by initial demyelinating changes and later by axonal degeneration[9,14] Donofrio et al suggested that arsenic may be primarily toxic to the neuronal cell body leading to axonal dysfunction that produces, initially, segmental demyelination (most apparent proximally) before axonal degeneration.[9] Toxic nodopathies such as tetrodotoxin poisoning or tick paralysis produce reversible conduction failure, apparent on NCS as conduction blocks mimicking demyelination.[50] It is possible that arsenic affects nodal conduction in the acute stages, before axonal degeneration becomes apparent.

Goebel et al identified arsenic deposits on spectrophotometric analyses of sural nerve biopsy specimens 2 months after exposure, but these findings were not present at 3 years.[48] The binding of arsenic to peripheral nerve tissue may explain continuing nerve degeneration even 3 months after exposure.[29] Several mechanisms, including oxidative stress, mitochondrial dysfunction, lipid peroxidation, and decreased acetylcholinesterase activity have been invoked to explain the neurotoxicity of arsenic.[2,51–53] Arsenic exposure reduced neurofilaments and decreased expression of fibroblast proteins in rat sciatic nerves, destabilizing and disrupting the cytoskeletal framework and potentially leading to axonal degeneration.[2,51,53–55] Kühn et al demonstrated a deficiency of thiamine during the acute encephalopathic phase in their patient treated with ATO and attributed the severe neurological complications to occult thiamine deficiency exacerbating neurotoxicity from ATO.[43] Lin et al hypothesized that thiamine deficiency contributed to the genesis of neurotoxicity in Taiwanese patients treated with ATO for urothelial carcinoma, based on their observation that supplementation with thiamine led to recovery from acute encephalopathy.[44] Jiang and Ji reported acute Wernicke encephalopathy and acute pancreatitis following ATO therapy of APL.[56] Pyruvate dehydrogenase, a component of the glycolytic pathway, requires thiamine as a cofactor and is sensitive to very small concentrations of trivalent arsenic derived from ATO, which binds to dihydrolipoate and other critical thiols and generates reactive oxygen species.[12,47,51,57] Adenosine triphosphate production is reduced through the process of arsenolysis, involving competition between inorganic arsenic and phosphate.[53] Exposure to ATO in the setting of thiamine deficiency therefore may affect neural tissues that are dependent on carbohydrates for energy production and cellular metabolism.[44]

Conclusion

ATO may potentially be associated with neurological toxicity, involving both the central and peripheral nervous systems. Close monitoring for peripheral neuropathy, myoclonus, and encephalopathy throughout ATO therapy is necessary, with early modification of the treatment protocol should toxicity be suspected. We believe that further study is needed to delineate the risk of central and peripheral nervous system complications of ATO therapy. Acute arsenic intoxication may present with an acute motor-predominant polyradiculoneuropathy that, given elevated CSF protein and suggestive findings on NCS, may be confused with GBS. The presence of encephalopathy or other organ system dysfunction and identification of potential arsenic exposure are important clues to investigate for possible intoxication. NCS findings in acute arsenic neuropathy follow a predictable course over weeks, ultimately resembling the more common chronic sensorimotor axonal form.

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Conflict of Interest
None declared.

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