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Groundwater:- A Familial Curse Sub-Acute Arsenic Poisoning Successfully Treated with Chelating Therapy:- A Case Report Series

Meena Dilip[1], Raghavi Abhilesh Bembey[2*], Mitakshara Chawla[3], Ajay Chauhan[4]

[1]PG Resident, Department of Medicine, ABVIMS & Dr. RML Hospital, New Delhi

[2]Senior Resident , Department of Medicine, ABVIMS & Dr. RML Hospital, New Delhi

[3]PG Resident,Department of Medicine, ABVIMS & Dr. RML Hospital, New Delhi

[4]Associate Professor and Consultant, Department of Medicine, ABVIMS & Dr. RML Hospital, New Delhi

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[*]**Corresponding author:** Raghavi Abhilesh Bembey, Senior Resident , Department of Medicine, ABVIMS & Dr. RML Hospital, New Delhi

ABSTRACT

Arsenic is a metalloid element and is notorious for causing toxicity in humans. Lower-dose chronic arsenic exposure can result in subacute toxicity that can include skin changes and skin cancer, peripheral sensorimotor neuropathy, diabetes mellitus, cardiovascular effects, peripheral vascular disease, hepatotoxicity, and other conditions. Sensory-motor polyneuropathy encompasses a spectrum of peripheral nervous system disorders with diverse clinical manifestations and etiologies, a rare one being arsenic toxicity. We present a case series of three members of a family who developed sensory-motor polyneuropathy at the same time. This case series highlights the unique presentations, diagnostic challenges, and rehabilitation considerations for this family caused by arsenic.

We present this case series of subacute poisoning of arsenic in the three members of a family of 10 members, all presenting with peripheral neuropathies, typical Mee's lines, and dermatological changes. This was a diagnostic challenge as it mimicked many common diseases like GBS, CIDP, etc. with a positive history of preceding loose stools and fever with no evident source of exposure. In the first case, a sensorimotor polyneuropathy with a demyelinating axonal variant was observed. This case presented with sensory deficits accompanied by predominant motor symptoms, distal more than proximal. The second case exhibited a sensory-motor variant, primarily manifesting with sensory symptoms distal more than proximal. In the third case, motor symptoms were prominent at presentation, along with evident demyelinating changes**.** Medical treatment was sought later due to various reasons and all patients had an incomplete recovery at discharge, but almost full recovery on follow-up. All the common sources of arsenic were explored and found to be increased in drinking water that was taken out through a hand pump. During the summer months, the only 3 members in the house were forced

to use the old deep tubewell in their house water for all their daily needs including cooking and drinking due to disruption in the municipality water supply to their house. Levels of arsenic in drinking water were significantly above the WHO safe limit for arsenic. Apart from their presentations, rehabilitation/physiotherapy and a review of literature is discussed in detail.

Keywords: Arsenicosis; Groundwater; Sensory-motor polyneuropathy; mee's line; DMSA; Dimercaprol

INTRODUCTION

Arsenic poisoning, a significant global public health concern, has been recognized for its diverse clinical manifestations, ranging from acute to chronic exposure. Arsenicosis, as defined by the WHO, is "a chronic health condition arising from prolonged ingestion of arsenic above the safe dose for at least 6 months, usually manifested by characteristic skin lesions of melanosis and keratosis, occurring alone or in combination, with or without the involvement of internal organs".[1] This review focuses on the relationship between arsenic poisoning and the development of polyneuropathy, a debilitating neurological disorder involving the peripheral nervous system.[2]

Subacute and chronic arsenic exposure, primarily through contaminated water, food, or occupational settings, has been linked to the development of polyneuropathy, characterized by sensory, motor, and autonomic dysfunction. The neurotoxic effects of arsenic are attributed to its interference with essential cellular processes, including oxidative stress, disruption of mitochondrial function, and impairment of cellular signaling pathways.[3] These mechanisms collectively contribute to axonal degeneration, demyelination, and subsequent nerve conduction abnormalities.

Clinical presentation of arsenic-induced polyneuropathy varies widely, ranging from mild sensory disturbances to severe motor deficits and pain. Diagnosis often involves a combination of clinical assessment, nerve conduction studies, hair and nail clippings, and measurement of urinary or blood arsenic levels. Treatment approaches primarily focus on the removal of the arsenic source, chelating existing arsenic in blood and excretion, supportive care, and symptomatic relief. However, reversing neurological damage remains a challenge.

Arsenic contamination of groundwater is not a new public health hazard and has been a threat to mankind in the last two to three decades in different parts of the world. It has been responsible for a large number of deaths. The groundwater can be contaminated naturally or by intense exploitation of groundwater, use of fertilizers, burning of coal, and leaching of metals from various textile industries.[4,5] Arsenic in deep tubewell water is mostly present in trivalent form, whereas in oxidative conditions as on the surface or in the ground, it gets converted into pentavalent arsenate. Preventive strategies are paramount in mitigating the impact of arsenic poisoning and associated polyneuropathy. Public health interventions, such as ensuring safe drinking water sources, regulating occupational exposure, and promoting awareness, are essential components of arsenic toxicity management.

CASE REPORTS

Case 1

A 31-year-old healthy, right-handed, married male, a computer operator by occupation and resident of Rama Vihar, Delhi, was in good health until about 2 months ago when he had an episode of undocumented fever with

chills and loose stools for about 3 to 4 days which got relieved with medicines. After this, he noticed a sudden onset of numbness in both his upper and lower limbs. The numbness was accompanied by weakness of his fingers, noticed as his fingers slipped on the keyboard while working on his computer, he also experienced difficulty holding his pen as it seemed to slip through his fingers but was able to carry out his other daily activities on his own.

Over a week, the patient experienced a gradual progression of numbness in both lower limbs. The symptoms first manifested in the feet, noticed by him as slipping off his slippers without him realizing. This forced him to frequently look down while walking to ensure his footwear remained in place. As the days passed, the numbness escalated. Over the next two weeks, the patient began experiencing a tingling sensation in both his hands and subsequently in both feet symmetrically. He also reported a history of experiencing burning pain in the soles of both feet making it difficult for him to walk, but the patient did not have any issues with perceiving the sensation of his clothing on various parts of his body. The weakness progressed in his hands to difficulty in writing, mixing food, buttoning –unbuttoning his shirt, and opening jars and all this led him to seek medical care. There were no previous instances of altered sensations related to hot or cold temperatures. Furthermore, there were no complaints of sensations resembling a tight band around a body part or sudden shocks upon bending the neck. The patient also did not report any complaints of backache or pain radiating from one area to another. Additionally, the symptoms did not worsen with actions such as coughing or sneezing.

The patient first reported at a local hospital wherein a Nerve Conduction Studies (NCS) was performed and was suggestive of both sensory and motor polyneuropathy. The underlying cause was not evaluated, keeping a differential of Guillain barre syndrome he was started on Intravenous Immunoglobulin (IVIG) twice in combination with pulse therapy but to no avail.

Moreover, during his week-long hospital stay, the patient's condition further deteriorated and he began to face difficulty in climbing stairs without support and difficulty in getting up from a sitting position. This weakness further intensified, making it challenging for him to stand up from a squatting position. Additionally, he experienced a sensation of falling with no preferential side of falling and knee buckling during walking.

As time progressed, he couldn't get out of bed without assistance, making him rely on his family members for basic daily activities. Within the following two weeks, he also encountered challenges turning over the bed and was then referred to our hospital. Despite these mobility challenges, it's noteworthy that he did not show symptoms of neck or respiratory muscle weakness.

Upon admission, a thorough medical examination was conducted on the patient. He was conscious, cooperative, and responsive to commands. His vitals were stable, and breathing at a rate of 16 breaths per minute in a normal abdomino-thoracic pattern, without using additional muscles. Single breath count of 27. On general physical examination, there was the presence of pedal edema and facial swelling. Notably, "Mees lines," which are transverse white bands on the nails, are observed in both the upper and lower nails [Figure 2]. Additionally, hyperpigmented scaly skin was observed on the anterior aspect of the legs [Figure 1].

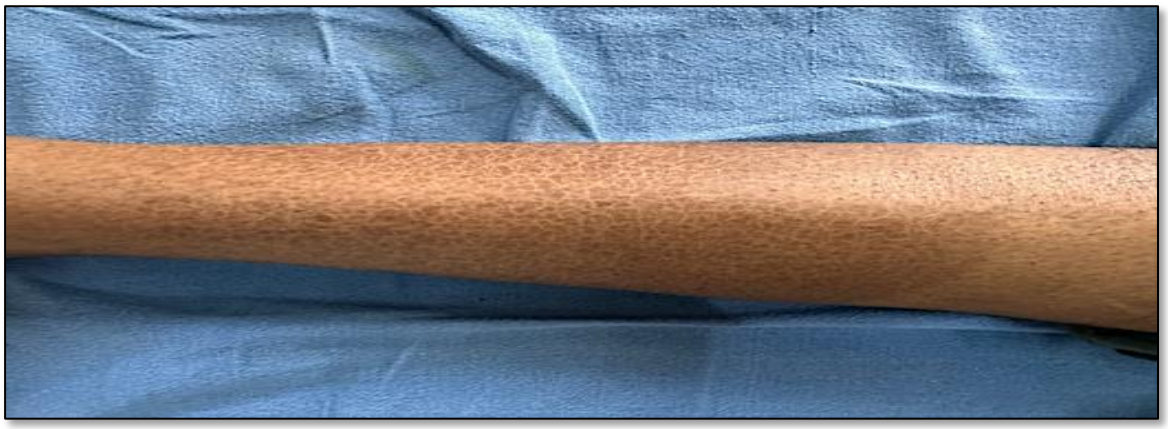
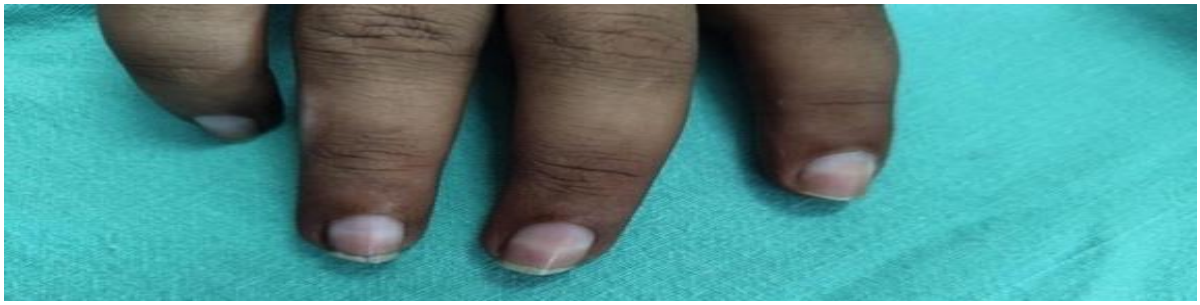


Figure 1: Hyperpigmented scaly skin was observed on the anterior aspect of the legs**.**



Fig*ure 2:* Mee's line.

In terms of motor examination, the patient exhibited complete claw hand deformity and bilateral foot drop. There was muscle wasting of the thenar and hypothenar muscles in the hands, as well as wasting of thigh muscles, although muscle bulk was symmetrically equal. Muscle tone was reduced in both upper and lower limbs. Muscle strength was notably impaired in different muscle groups: neck (3/5), wrist (3/5), hand grip (poor), elbow (4/5), shoulder (4/5), ankle (0/5), knee (2/5), and hip (3/5). Truncal (core) weakness was also present.

Abdominal and all deep tendon reflexes (DTR) were reduced. The plantar reflex was mute but painful. On sensory examination, the patient showed reduced perception of fine touch, joint position sense, proprioception, and vibration in both upper and lower limbs. The patient underwent investigations to further diagnose the neurological symptoms. All his routine investigations were normal. The investigation included a cerebrospinal fluid (CSF) analysis which was suggestive of albumino-cytological dissociation. Nerve conduction velocity

(NCV) studies suggested sensory with sural nerve involvement and motor involvement, pointing towards a demyelinating and axonal polyneuropathy, possibly caused by a secondary factor.

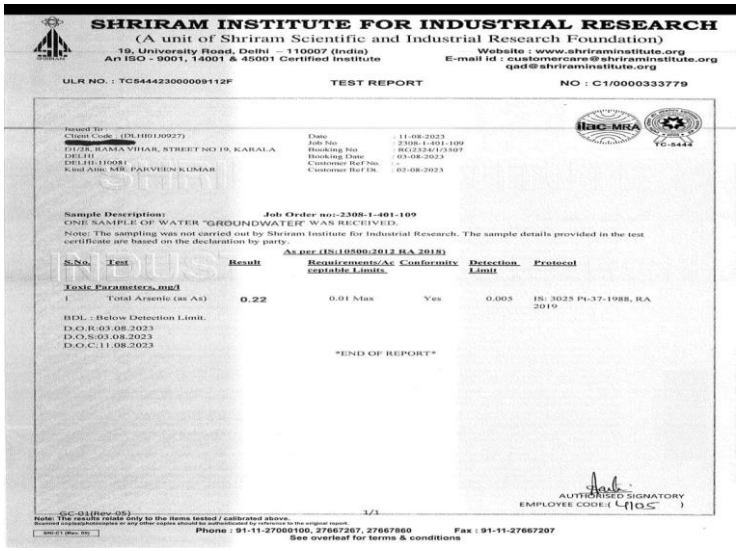
We planned to conduct a sural nerve biopsy, given the involvement of the sural nerve and suggestive of axonal degeneration pathology. The initial treatment approach involved intravenous immunoglobulin (IVIG) followed by oral steroid therapy, with a presumed diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

However, the patient's condition did not significantly improve with the above treatments, prompting the medical team to consider arsenic poisoning as a possible cause due to a family history of the same complaints and the presence of peripheral signs that were highly indicative of arsenic poisoning, and a 24-hour urine arsenic level done confirmed elevated levels (67.47ug/liter) above the normal reference value (less than 35ug/liter). Consequently, the patient was managed with an antidote therapy involving the administration of DMSA (Dimercaptosuccinic acid) for three days. While reviewing source of arsenic, all utensils used in the household were examined, but high level of arsenic was detected in the groundwater from the subject's house (Figure 5), which they had been using for pat 3 months when the municipal water supply was abrupted.

After the antidote treatment, the patient's sensory and motor symptoms improved. Specifically, muscle strength increased to 4/5 at the neck, hip, and knee, and 3/5 at the ankle. Following this improvement, the patient was discharged with oral steroid therapy and received advice for appropriate physiotherapy. Regular follow-up was also recommended to monitor the patient's progress. On 1 month follow up patients showed significant improvement with decreasing urine arsenic levels (Figure 3). On 3 months follow-up, the patient's urine arsenic levels became undetectable, he regained his power completely with no neurological deficit and was able to perform all his daily activities, starting with his job and disappearance of mees lines (as shown in Figure 3), however, his repeat NCV was still suggestive of motor-sensory neuropathy in all four limbs. Several photos (Figure 3 & 4) from the patient's routine follow-up clearly indicate significant recovery following the treatment.

Figure 3: Disappearance of Mees line on follow up

Figure 4: a) complete recovery of power on follow up, b) intermediate follow up picture of patient wherein patient needed support to stand and lift hands.



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Date : 11-08-2023
Job No : 2308-1-401-109
Booking No : RG2324/1/3507
Booking Date : 03-08-2023
Customer Ref No. : -
Customer Ref Dt. : 02-08-2023

Sample Description: Job Order no:-2308-1-401-109
ONE SAMPLE OF WATER "GROUNDWATER" WAS RECEIVED.
Note: The sampling was not carried out by Shriram Institute for Industrial Research. The sample details provided in the test certificate are based on the declaration by party.

As per (IS:10500:2012 RA 2018)

S.No.	Test	Result	Requirements/Acceptable Limits	Conformity	Detection Limit	Protocol
Toxic Parameters, mg/l						
1	Total Arsenic (as As)	0.22	0.01 Max	Yes	0.005	IS: 3025 Pt-37-1988, RA 2019

BDL : Below Detection Limit.
D.O.R:03.08.2023
D.O.S:03.08.2023
D.O.C:11.08.2023

END OF REPORT

AUTHORISED SIGNATORY
EMPLOYEE CODE : (1085)

GC-01(Rev-05) 1/1
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Figure 5: Report showing high levels of arsenic in groundwater from subject's house.

Case 2

A 67-year-old male, father of the previous case, a known case of hypertension (HTN), coronary artery disease (CAD) post PTCA on regular treatment had complaints of fever and vomiting about 2 weeks after the first case, now presented with tingling and numbness for the past 4 weeks and weakness in both his upper and lower limbs for the last two weeks.

The patient began experiencing sensory symptoms in the lower limbs, initially noticing slippage of slippers without being aware. The symptoms progressed to the hands and eventually affected areas up to the knees and

elbows bilaterally. Two weeks after the onset of sensory disturbances, the patient reported weakness in both the upper and lower limbs. In the lower limbs, this manifested as difficulty gripping slippers. In the upper limbs, he struggled with daily tasks like buttoning/unbuttoning his shirt and using a toothbrush. However, the patient was still able to walk with support, squat, and rise from a chair or bed without any history of falling.

The patient's examination revealed stable vital signs, the presence of Mees lines (white bands) on the nails, and hyperkeratosis and hyperpigmentation on the soles of the feet. Central nervous system (CNS) examination showed sensory deficits (loss of fine touch/vibration sensation up to the knees and wrists) and reduced muscle strength (4/5 in upper limbs, 3/5 at ankle, 4/5 at knee and hip) with absent reflexes in upper and lower limbs. Further investigations included nerve conduction studies (NCS) indicating sensory-motor neuropathy in the affected limbs, likely due to both demyelination and axonal degeneration. Cerebrospinal fluid (CSF) analysis suggested albumino-cytological dissociation. A 24-hour urine test showed an arsenic level of 43.87ug/liter. The patient was planned for a sural nerve biopsy due to sural nerve involvement observed in the NCS study which showed axonal degeneration. The patient initially received treatment with IVIG in line with CIDP and oral prednisolone but showed no symptom improvement at all even after two weeks. Consequently, we administered **British anti-Lewisite (dimercaprol**) following the standard protocol. Upon reassessment two weeks post-discharge, the patient exhibited improvements in both motor and sensory symptoms. Repeat urine 24 hr arsenic levels after 2 weeks showed reduced urinary arsenic levels (19.19 mcg/L).

Case 3

The third patient from the same family, 27 years healthy female noticed mees lines on her nail after our medical team persuaded them to monitor and look for signs and symptoms of arsenic poisoning in other members and neighbors. On history taking she also had a previous history of fever and vomiting 1 month back, now had complaints of weakness in both upper limbs without any sensory, autonomic, or respiratory symptoms, and the patient was able to do daily routine activities. On examinations vitally stable, and general physical examinations, mees lines were present. Neurological examinations revealed absent reflexes in upper limbs with intact motor and sensory systems. On NCS study was suggestive of demyelinating degeneration. Urine 24-hour arsenic level was sent for the same which came out to be positive [70.26 ug/liter]. The patient was managed with DMSA Therapy and discharged with advice to follow up. Follow-up showed undetectable arsenic levels in urine and disappearance of mees line.

Informed detailed consent was taken from all the patients to share the data. The local authorities were informed about the high arsenic levels in the deep tubewell and the needed actions are being undertaken by them.

DISCUSSION

Arsenic poisoning can result from ingestion of trivalent arsenite in various available forms. A large number of the population in India, Pakistan, and certain other countries are chronically exposed to naturally occurring arsenic in groundwater. Some uncommon sources with chances of accidental exposure include burning preservative-impregnated wood and storing food in antique copper kettles.[6]

Arsenic is absorbed in the small intestine and on entering the circulation undergoes hepatic metabolism to produce less toxic forms of arsenic (monomethylarsonic acid and dimethylarsinic acid). Approximately 50% of ingested arsenic is excreted via the kidneys in 3–5 days. In chronic exposure, arsenic accumulates in the heart, kidneys, liver, and lungs, with smaller amounts in the gastrointestinal tract, muscles, nervous system, and spleen.[7] After two weeks of chronic exposure deposits also occur in the hair and nails.

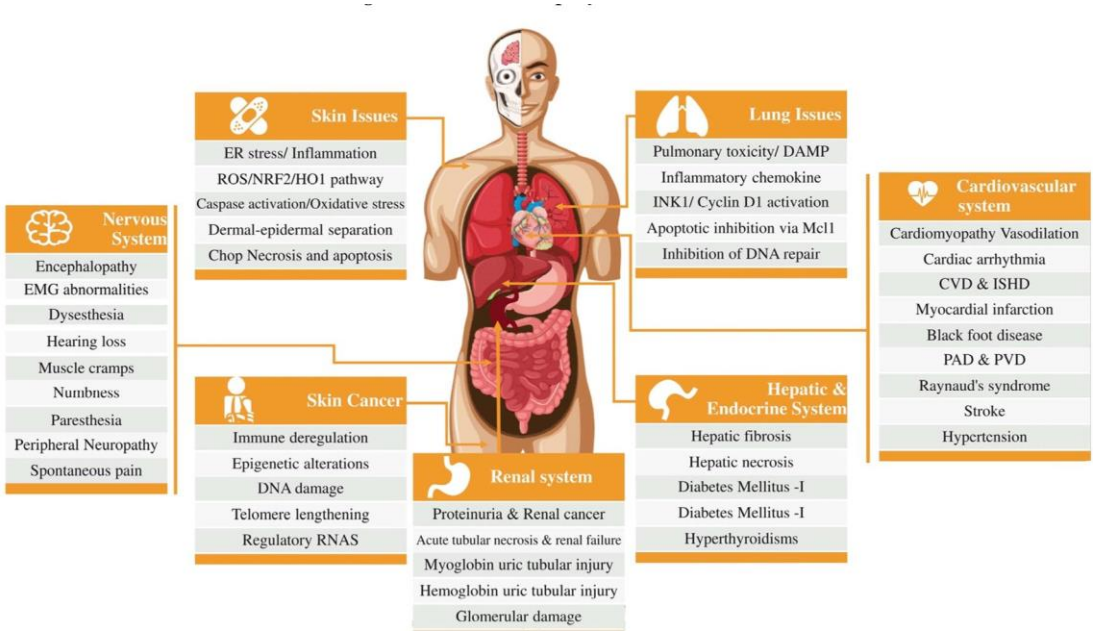

Figure: Impact of prolonged arsenic exposure on human body.

Acute arsenic exposure usually presents with gastrointestinal manifestations of nausea, vomiting, abdominal pain, and loose stools thereby leading to hypotension, tachycardia, and vasomotor collapse. Chronic arsenic toxicity can manifest as demyelinating polyradiculopathy with a close resemblance to Guillain Barre Syndrome and becomes a close differential of the same. Early clinical suspicion and confirmation are essential to initiate appropriate therapy for the patient and for the introduction of chelators such as British anti-lewisite (BAL) and Dimercaprol (DMSA). However in our cases even with the exposure being subacute, we gave a trial of chelating agents after obtaining detailed consent from the patient and family, to achieve a great response to chelating therapy even in sub-acute poisoning.[8]

Arsenic neuropathy is considered a distal axonopathy possibly related to the binding of arsenic to dihydrolipoate, a sulfhydryl component of the pyruvate dehydrogenase complex required for the oxidation of pyruvate. Histological studies of peripheral nerves mostly demonstrate axonal degeneration with the predominant involvement of the large myelinated fibers.

Arsenic is a geogenic, insipid, transparent, and odorless toxic metalloid. When arsenic concentration in groundwater surpasses the drinking water threshold established by the World Health Organization by a factor of 10 µg/L, it results in arsenic-enriched groundwater. The presence of arsenic in groundwater has been associated

with a range of adverse health effects, such as keratinization of the skin, hyperpigmentation of the palms and soles, arsenicosis, hyperkeratosis, coronary heart disease, bronchiectasis, Bowen's disease, etc. And is also a group A carcinogenic agent. The hydrogeochemical properties of groundwater with elevated levels of arsenic indicate that the origins and movement mechanisms are linked to multiple factors, such as the dissolution of arsenic-bearing minerals, the redox reaction between arsenic-bearing sulfides and arsenic-bearing Fe/Mn-oxyhydroxides with the groundwater, the adsorption/desorption mechanism, the role of mineral phases (e.g., Fe/Mn oxide and hydroxide, arsenopyrite, arsenate, siderite, goethite, rhodochrosite), and groundwater extraction.[9]

CONCLUSION

In this case series, crowding of 3 cases within a family with similar presenting complaints and findings raised the suspicion of chronic exposure most likely from a common water source. For a patient presenting with gastrointestinal manifestations followed by features of peripheral neuropathy the possibility of Arsenic toxicity should be kept into consideration owing to increased risk of exposure in the Indian setting. Clinical presentation mimicking GBS with no response to standard IVIG, Plasmapheresis with progression of illness despite therapy, and a possibility of toxin exposure more likely Arsenic, Thallium is to be taken into consideration. The delay in diagnosis, diagnostic challenges faced, and progression of illness if not immediately managed predisposes the patient to permanent disability due to atrophy and wasting of muscles.

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