A Guillain-Barré Syndrome-like Neuropathy Associated with Arsenic Exposure

Sunyoung Kim¹, Akito Takeuchi², Yaeko Kawasumi³, Yoko Endo⁴, Heun Lee⁵ and Yangho Kim⁶

¹Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Republic of Korea, ²Osaka Occupational Health Service Center, Japan Industrial Safety and Health Association, Japan, ³Occupational Health Research and Development Center, Japan Industrial Safety and Health Association, Japan, ⁴Research Center for Occupational Poisoning, Kansai Rosai Hospital, Japan Labour Health and Welfare Organization, Japan and ⁵Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Republic of Korea

Abstract: A Guillain-Barré Syndrome-like Neuropathy Associated with Arsenic Exposure: Sunyoung Kim, et al. Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Republic of Korea—Objectives: We report on a patient presenting with an isolated polyneuropathy mimicking Guillain-Barré syndrome (GBS) associated with arsenic exposure. Case: A 43-year-old man visited our emergency room complaining of progressive quadriparesis over the prior 5 days. His clinical course with laboratory data was typical of GBS. However, because of his recent use of herbal medication, we screened for the presence of several heavy metals. Serial analyses of urinary inorganic arsenic concentrations confirmed exposure to arsenic. He was diagnosed as arsenic neuropathy mimicking GBS without any systemic manifestation of arsenic intoxication. Conclusions: The present case study emphasizes the need to consider arsenic intoxication in patients presenting with acute demyelinating neuropathies and histories of herbal medication use.

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Acute arsenic intoxication is a rare cause of acute demyelinating polyneuropathy¹. The earliest clinical features of acute, high-dose arsenic poisoning reflect multiorgan involvement and often include acute gastroenteritis variably associated with encephalopathy, pancytopenia, hepatitis, cardiomyopathy and dermatitis², ³. However, chronic low-level arsenic exposure may cause distal axonopathy, predominantly sensory polyneuropathy, that is not preceded by multiorgan involvement², ⁴. The acute neuropathy is usually initially misdiagnosed as Guillain-Barré syndrome (GBS); the electrophysiological and spinal fluid examination data support such a diagnosis⁵. Several cases of acute arsenic neuropathy mimicking GBS have been reported, with all patients exhibiting severe motor-sensory polyneuropathy and various systemic manifestations. Herein, we report an isolated GBS-like neuropathy associated with arsenic exposure.

Case presentation

A 43-year-old man visited our emergency room complaining of progressive quadriparesis over the prior 5 days. Previously, he had been healthy. For 25 days prior to admission he had consumed a herbal medication for treating psoriasis. Five days after ceasing to take this medication, he experienced bilateral arm weakness and hand paresthesia. Weakness in both legs developed 2 days later, and finally, he found it difficult to raise either arm, to walk and to climb steps. His blood pressure was 130/77 mmHg, and his pulse was 59 beats per minute and regular. No cutaneous abnormality, such as maculopapular scaly rash or Mee’s line, was evident. Neurological examination revealed moderate proximal dominant symmetric arm and leg weakness. No cranial nerve sign was present, and his mentality was not altered. Reflexes were brisk in the arms but reduced in the knees and ankles.
He complained of mild paresthesia in his feet and hands, but no impairment in distal vibration or joint position sense was evident. Laboratory data were as follows: Hemoglobin 15.9 g/dl, white blood cell (WBC) 12,800/mm³ with 1% eosinophils, aspartate aminotransferase (SGOT) 23 IU/l and alanine aminotransferase (SGPT) 39 IU/l. Test results for hepatitis-associated antigen, antinuclear antibody and a serum Veneral Disease Research Laboratory test (VDRL) were all negative. IgG and IgM antibodies to Herpes simplex, Mycoplasma pneumonia and human T-cell lymphoma virus type I and II were negative. Polymerase chain reaction for tuberculosis and Herpes simplex virus type I and type II produced normal results.

Vitamin B-12 and folate serum levels were normal. No anti-ganglioside M1 (anti-GM1) antibodies or anti-ganglioside D1 (anti-GD1) antibodies were detected. Spinal fluid examination revealed no WBCs; the protein level was 56.2 mg/dl. Electrodiagnostic studies revealed the presence of an acquired demyelinating polyradiculoneuropathy. The median peroneal nerve revealed no F-wave and increased terminal latency was evident. The median and ulnar nerves showed only mild reductions in distal motor amplitudes, and conduction blocks were evident. Electromyography showed that the recruitment patterns were discrete. Spontaneous activity was not noted, and no evidence of reinnervation was found. We diagnosed GBS, possibly associated with a recent viral infection of uncertain etiology. He was treated with 0.4 g/kg/day of intravenous immunoglobulin (IVIG) for 5 days and responded with a clear improvement in limb strength.

At the Occupational Health Research and Development Center, Japan Industrial Safety and Health Association, in Japan. However, a sample of the relevant herbal medicine was not available. Informed consent was obtained from the patient.

**Determination of arsenic compounds in urine**

The arsenic compounds in urine were analyzed using an Agilent 1100 HPLC (Agilent Technologies, Santa Clara, CA, USA) and an Agilent 7700x ICP-MS (Agilent Technologies, Santa Clara, CA, USA) to separate arsenic species and to detect such species, respectively. Urine was diluted five-fold with ultrapure water and filtered through a cellulose filter 0.45 µm in pore size (Minisart C15; Sartorius Stedim, Germany). Arsenite (AsIII), arsenate (AsV), monomethylarsenic acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine (AsBe) were separated by HPLC using an anion-exchange column (IonPac AS22, 250 mm × 4.0 mm internal diameter; Dionex, Sunnyvale, CA, USA). The mobile phase was 20 mM NH₄HCO₃ (pH 10.0), and the flow rate 1.0 ml/min. The ICP-MS detector was set to m/z 75 for ³²As⁺ and m/z 77 for argon chloride (⁴⁰Ar⁷Cl⁻). The detection limits for AsIII, AsV, MMA, DMA and AsBe were 0.3, 0.2, 0.2, 0.3 and 0.3 µg As/l, respectively.

The urinary arsenic concentrations measured on the second day of hospital stay (HD 2) are shown in Table 1. These are values obtained 1 wk after cessation of herbal medicine treatment. The total concentrations of inorganic arsenic and methylated metabolites thereof (MMA plus DMA) were above 35 µg As/l of the ACGIH BEI¹. In addition, the sum of the concentrations of arsenic and MMA was high; this value on HD 7 and HD 12 fell compared to that on HD 2.

**Discussion**

Humans may be exposed to both organic and inorganic arsenic compounds. Contaminated drinking water and food are the main sources of inorganic arsenic, such as arsenite and arsenate⁶. Organic arsenic compounds including arsenobetaine and arsenosugars are derived mainly from seafood⁷. Inorganic arsenic compounds are metabolized to MMA and DMA and are excreted in the urine together with unchanged compounds.

Table 1. Arsenic species in urine (µg As/l) after cessation of herbal medicine treatment

<table>
<thead>
<tr>
<th>Sample</th>
<th>AsIII</th>
<th>AsV</th>
<th>MMA</th>
<th>DMA</th>
<th>Arsenobetaine</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD 2</td>
<td>6.4</td>
<td>ND</td>
<td>8.9</td>
<td>77.5</td>
<td>402.6</td>
<td>12.5</td>
<td>507.9</td>
</tr>
<tr>
<td>HD 7</td>
<td>3.2</td>
<td>ND</td>
<td>3.7</td>
<td>26.5</td>
<td>57.6</td>
<td>9.1</td>
<td>100.1</td>
</tr>
<tr>
<td>HD 12</td>
<td>3.7</td>
<td>ND</td>
<td>3.9</td>
<td>32.1</td>
<td>57.6</td>
<td>ND</td>
<td>97.3</td>
</tr>
</tbody>
</table>

The totals are the sums of the levels of all detected arsenic compounds.
inorganic arsenic\textsuperscript{8}. Thus, 35 µg As/l, the sum of the levels of inorganic arsenic, MMA and DMA in urine, has commonly been used as a biomarker of inorganic arsenic exposure by the ACGIH\textsuperscript{5}. Most fish and shellfish are rich in arsenobetaine, which is rapidly excreted (unchanged) in the urine and is a principal contributor to the total urinary arsenic level. Seaweed and some seafood, including scallops and mussels, are also rich in arsenosugars, which are metabolized to several compounds (mainly DMA) that also contribute to total urinary arsenic levels\textsuperscript{9}. Consequently, the total urinary arsenic concentration, and that of arsenobetaine, may differ greatly when levels in Western countries, and Japan or Korea, are compared. Arsenic concentrations in general populations (the sums of the levels of inorganic arsenic, MMA and DMA in the urine) are approximately 10 µg/l in European countries and the USA but about 50 µg/l in Japan\textsuperscript{8}. Some of the difference between the levels of Western countries and those of Japan or Korea may be attributable to among-country variation in the levels of consumption of seaweeds and some types of seafood, including scallops and mussels. These foods are rich in arsenosugars that are metabolized to DMA\textsuperscript{10}. Therefore, the concentration of inorganic arsenic or MMA may be more useful in assessment of exposure to inorganic arsenic than the sum of the levels of inorganic arsenic, MMA and DMA\textsuperscript{10}.

On HD 2, the total concentration of inorganic arsenic and methylated metabolites thereof (92.8 µg As/l) was above the 35 µg As/l set as the ACGIH BEI. In addition, the sum of the concentration of inorganic arsenic and MMA is considered to be a good biological indicator of inorganic exposure among people generally taking seafoods\textsuperscript{11}. The sum (15.3 µg As/l) of the AsIII and MMA concentration of HD 2 was higher than 95th percentile of the general population (12.6 µg/l), but those on HD 7 and HD 12 were almost the 75th percentile\textsuperscript{11}. In particular, an MMA level higher than that of inorganic arsenic indicates inorganic exposure based on inorganic arsenic metabolism\textsuperscript{12}.

The concentrations of arsenic compounds were lower on HD 7 and HD 12 compared with those on HD 2. Further, the peak concentrations may have been eight-fold higher than the concentrations measured 1 week after cessation of herbal medication, when it is considered that the biological half-life of urinary total arsenic is approximately 60 h\textsuperscript{12}. Therefore, our patient may have been exposed to very high levels of inorganic arsenic.

The source of arsenic in the present instance was presumed to be a herbal medicine; such Korean medicines have been previously reported to contain arsenic\textsuperscript{13, 14}. We could not directly confirm this hypothesis because we could not obtain a sample of the relevant medicine.

The most frequent neurological complication induced by arsenic poisoning is symmetrical sensory-motor polyneuropathy featuring more distal impairment\textsuperscript{15}. The most prominent electrophysiological findings are marked abnormalities in both sensory and mixed nerve conduction and moderate abnormalities in motor conduction\textsuperscript{15}. In addition to the classic presentation of chronic axonal polynuropathy, acute or subacute demyelinating polyneuropathy commencing 1–3 wk following arsenic exposure has been described\textsuperscript{11}. Such acute neuropathy is usually initially misdiagnosed as GBS; the electrophysiological and spinal fluid data support such a diagnosis. This was true of the present case; we first diagnosed GBS because the clinical course and the laboratory data were typical of GBS. The patient presented with acute progressive motor weakness, demyelinating polyneuropathy and albuminocytologic dissociation. However, because of his recent use of a herbal preparation, we screened for the presence of arsenic, and thus serial analyses of inorganic arsenic concentrations confirmed exposure to arsenic. In particular, the temporal relationship between use of the herbal medication and development of motor weakness caused us to suspect arsenic intoxication. We also ruled out GBS-related viral diseases such as Herpes simplex, Mycoplasma pneumoniae and human T-cell lymphoma virus type I and II.

Notably and unlike what was found in previously reported instances of arsenic neuropathy mimicking GBS\textsuperscript{11}, our present patient showed mild neuropathy in the absence of any systemic manifestation of arsenic intoxication. We presume that the severity of neuropathy and the existence of systemic symptoms depend on both the level of toxic material ingested and the duration of exposure. In addition, host factors, such as individual variability in the hepatic P450 system, may play a role in determining the severity of neuropathy and clinical manifestations. The exact pathophysiology of arsenic toxicity is not known, but it has been suggested that arsenic is primarily toxic to the cell body; segmental demyelination occurs prior to axonal degeneration\textsuperscript{11}. Taken together, this neuropathy is possibly due to arsenic poisoning, although a causal relationship between arsenic exposure and a GBS-like neuropathy was not determined. Any history of arsenic exposure such as a history of herbal medication use in a peripheral neuropathy should raise a suspicion of arsenic poisoning.

However, the present work has some limitations. First, we could not identify arsenic in a sample of the herbal medicine, although our serial analyses of the inorganic arsenic concentration (and the levels of its methylated metabolites) constitute evidence of expo-
sure to arsenic. Second, we could not completely rule out a real causal pathogen that might have existed in the herbal medicine or from some unknown origin. One example would be a plant-derived phorbol ester that can reactivate latent virus in the body, which could be the real cause of GBS in this case.

In summary, we presented a GBS-like neuropathy associated with arsenic exposure. Serial species analyses of urinary inorganic arsenic concentrations confirmed exposure to arsenic. The temporal relationship between use of the herbal medication and development of motor weakness was also shown. This peripheral neuropathy was possibly due to arsenic poisoning, although a causal relationship between arsenic exposure and GBS was not determined.

References