CASE REPORTS

Toxic neuropathy following ingestion of self-collected herbs Psychotria rubra

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Abstract

A case of human neurotoxicity after ingestion of self-collected Psychotria rubra, a herb used in Southern China for typhoid, is reported. Psychorubin, a naphthoquinone derivative isolated from Psychotria rubra, was the possible inducing agent. The electrophysiological and histopathological findings were suggestive of a demyelinating neuropathy with predominant proximal involvement. The patient recovered completely after six months. Some issues in the use of self-collected herbs are discussed.

Key words: Neurotoxicity, Chinese herbs, Psychotria rubra, naphthoquinone

INTRODUCTION

Chinese medicinal herbs are commonly used in Oriental and Western countries.1,2 Side-effects from herbs include toxicity from herbal ingredients or contaminants, hypersensitivity, and interactions with Western pharmaceutical agents3 or between different herbal species.4 The exact mechanisms are often ill-understood since medicinal herbs are used in combinations which contain multiple and variable quantities of therapeutic and non-therapeutic ingredients, many of which are unknown or their actions are unknown. Neurological manifestations include optic neuritis, peripheral neuropathy, and encephalopathy. We report an unusual case of poisoning due to Psychotria rubra (Figure 1).

FIG. 1: A fresh specimen of Psychotria rubra.

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CASE REPORT

A 48-year-old Chinese male driver with no past medical illness presented with progressive diplopia and unsteadiness of gait over two days. He was well-nourished and was a non-drinker. Five days prior to admission, he started taking a herbal remedy as a tonic. Before that, he was completely asymptomatic and was on no other medication. The herbs were collected by his mother, a housewife, from the non-agricultural countryside of Lantau, an offshore island of Hong Kong.

The patient was fully conscious and afebrile. Ocular movements were restricted with diplopia in all directions and bilateral nystagmus that was worse on left gaze. The other cranial nerves were intact. He walked with a wide-based gait and there was bilateral limb ataxia, more marked on the left side, as well as truncal ataxia. The limbs were hypotonic with hyporeflexia. Plantar responses were normal. Power was full in all muscle groups. Perception of all sensory modalities were diminished in the trunk and limbs. Sphincter functions were preserved. The rest of the physical examination was unremarkable.

Five species of plants were identified in a fresh specimen of the unprocessed herbs - A) Ficus hirta, B) Ilex asperella, C) Rubus parvifolius, D) Embelia laeta, and E) Psychotria rubra. They looked clean and free from fungal contamination. A few pieces of the roots of each plant were used in the preparation. A broth was made with Ficus hirta and about 200 grams of pork. Ilex asperella, Rubus parvifolius, Embelia laeta, and Psychotria rubra were boiled with three bowls (approximately 150 ml/bowl) of water to concentrate into one bowl of concoction. Both were taken once daily.

Routine blood count, liver and renal functions, vasculitic screen, and serial viral serology were non-contributory. Heavy metals, vitamin-deficiencies, and porphyria screening were negative. Cerebrospinal fluid (CSF) analyses performed on the sixth day after onset revealed normal cell count and biochemistry. The protein level was 32 mg/dl. Oligoclonal band was absent and immunoglobulin levels were not elevated. Microbiological studies showed no evidence of infection. Magnetic resonance imaging of the brain and brainstem were normal.

Electrophysiological studies performed ten days after admission [Table 1] showed a moderate reduction in peak-to-peak sensory action potential amplitudes in the hands with preserved peak latencies. Distal motor latencies,

| TABLE 1: Electrophysiological findings 12 days after the onset of symptoms. |
|--------------------------|-----------------|-----------------|-----------------|-----------------|
|                          | Rt. median      | Rt. ulnar       | Rt. sural       | Lt. sural       |
| SNAP Amplitude           | (µV)            |                 |                 |                 |
|                         | 9.7             | 4.1             | 21.5            | 20.4            |
| SNAP peak latency        | (ms)            |                 |                 |                 |
|                         | 3.1             | 2.7             | 2.6             | 2.9             |
|                          |                 |                 |                 |                 |
|                          | Rt. median      | Rt. ulnar       | Rt. CP          | Lt. tibial      |
| DML                     | (ms)            |                 |                 |                 |
|                         | 3.1             | 2.7             | 4.3             | 4.5             |
| MMCV                    | (m/s)           |                 |                 |                 |
|                         | 53.0            | 51.0            | 51.0            |                 |
| CMAP Amplitude          | (mV)            |                 |                 |                 |
|                        | 9.3             | 6.4             | 10.6            | 10.7            |
| Stimulate               | wrist           | wrist           | ankle           | ankle           |
| Record                  | APB             | ADM             | EDB             | AH              |
| F-persistence           | 12.5%           | 12.5%           | 81.3%           |                 |
| F-wave ML               | 24.5            | 28.7            | 42.3            |                 |

(SNAP = Sensory nerve action potential, CP = Common peroneal, DML = Distal motor latency, MMCV = Maximum motor conduction velocity, CMAP = Compound motor action potential, APB = Abductor pollicis brevis, ADM = Abductor digiti minimi, EDB = Extensor digitorum brevis, AH = Abductor hallucis, ML = Minimal latency.)
maximum motor conduction velocities, and motor action potential amplitudes were normal. F-persistence was significantly reduced over the median and ulnar nerves with normal F-wave minimal latencies but dispersed responses. These findings were suggestive of an evolving proximal radiculoneuropathy, more pronounced in the upper limbs.

Sural nerve biopsy was performed three weeks after the onset. There were no lymphocytic infiltrate or vasculitis. Ultrastructural examination revealed myelin irregularity in many large myelinated fibres, with loosening and early disintegration. Others had abnormally thin myelin sheaths which was indicative of the remyelinating phase after an episode of demyelination. Occasional macrophages were seen in the interstitium. Onion bulb was absent. Axonal degeneration change was not prominent. The overall features were those of an acute demyelinating neuropathy.

The patient remained stable after discontinuation of the herbs. Reassessment after three months showed intact coordination and normal gait with residual hyporeflexia and restriction of left eye adduction, which subsequently resolved at six months.

DISCUSSION

The histopathological and electrophysiological evidence indicated a predominantly proximal demyelinating polyneuropathy. The patient also had clinical features suggestive of brainstem nuclei and cerebellar connections involvement.

Guillain-Barre syndrome (GBS) or Miller-Fisher syndrome can present similarly. However, the patient had no infection prior to the onset of his complaints and viral serology was negative. CSF protein was normal, although this is possible in GBS. In the nerve biopsy, lymphoid infiltrate characteristically found in GBS was absent. Paraneoplastic syndromes can also manifest as demyelinating neuropathies, but no malignancy was identified and the neurological defects were self-limiting.

Apart from the herbs, there was no exposure to other drugs or toxins. The plants were collected from a non-agricultural region making pesticide poisoning unlikely. There is no reported neurotoxicity associated with Ficus hirta, Ilex asperella, Rubus parvifolius and Embelia laeta or their ingredients. This particular case took place during a mini-epidemic of neuropathy caused by a contaminant from the root of Podophyllum hexandrum2 and some of the neurological manifestations were similar to those of podophyllin-poisoning. We questioned him specifically and confirmed that he did not take the contaminant, which was available only through importation from Mainland China.

Psychorubrin, a naphthoquinone derivative, was isolated from Psychotria rubra. Psychotria rubra is known in Chinese as 山大刀 (山大刀), 九节木 (九节木), 刀伤木 (刀伤木), 大丹叶 (大丹叶), and 山公 (山公). Naphthoquinones are vitamin-K related quinone-based xenobiotics. These are often used for inducing in-vitro oxidative stress in cellular experiments. Menadione (2-methyl-1,4-naphthoquinone), Juglone (5-hydroxy-1,4-naphthoquinone), and 2,3-dimethoxy-1,4-naphthoquinone are commonly used agents. Other naphthoquinone derivatives also exhibit similar oxidative properties. As naturally occurring compounds, naphthoquinones are present in many plants which, when ingested, can induce toxicity. The proposed mechanisms of cytotoxicity include free radical generation through redox cycling, depletion of NAD+, depletion of glutathione, and inhibition of cell growth and acceleration of apoptosis. A dose-dependent, self-limiting demyelinating neuropathy affecting the spinal roots and proximal nerves was induced experimentally in Sprague-Dawley rats treated with CGS21595, a naphthoquinone derivative. The histological findings included demyelination with occasional areas of remyelination, and infiltration by macrophages. Recovery was complete after several weeks.

After exclusion of other causes of neuropathy, the possible pathogenic mechanism in our patient could be naphthoquinone-induced neurotoxicity. The onset of symptoms soon after consumption of Psychotria rubra, the electrophysiological picture of proximal neuropathy, the histopathological findings and the clinical course similar to the CGS21595-treated Sprague-Dawley rats, were all supportive of the postulated casual relationship. However, the quantity of the naphthoquinone ingested was relatively small as compared with the experimental model, and so was the duration of exposure. Further animal studies using Psychorubrin is needed to prove our postulation.

Psychotria rubra is commonly found in the shrub forests of southern China. Both the root and leaves are utilised as medicinal herb for their anti-inflammatory properties. Powder grounded from dried roots and leaves are used for typhoid. The leaves are prepared as a decoction for dysentery, or used as a poultice for fractures, joint pain, leg ulcers, and snake
bites. The use of self-collected herbs for common ailments is a popular practice in South East Asia, especially in the rural regions where Western doctors or qualified herbalists cannot be afforded. Remedies are often passed on from memory, and the plants are identified, collected and processed by untrained or semi-trained farmers. This kind of amateur practice is particularly dangerous. Erroroneous identification may result in the selection of unintended agents causing serious toxicity. Inappropriate processing may not inactivate or remove the toxic ingredients. Excessive dosage or duration of treatment can also contribute to toxicity. A better understanding of the potential toxicity of commonly used agents is essential to avoid adverse therapeutic outcomes.

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