Chronic Bromvalerylurea Intoxication: Dystonic Posture and Cerebellar Ataxia due to Nonsteroidal Anti-inflammatory Drug Abuse

Tadataka Kawakami, Yoshihisa Takiyama, Ichiro Yanaka, Tomohiro Taguchi, Yasufumi Tanaka, Masatoyo Nishizawa and Imaharu Nakano

Nalon-Ace® and other nonsteroidal anti-inflammatory drugs (NSAID) containing bromvalerylurea (BVU) are sold as over-the-counter (OTC) drugs and are obtainable without prescription in Japan. A 32-year-old woman was diagnosed as having chronic BVU intoxication due to habitual use of Nalon-Ace®. In addition to cerebellar ataxia and pyramidal signs well known in this condition, she showed an as yet non-described dystonic posture of the neck. Laboratory tests revealed an elevated concentration of serum organic bromide, iron deficiency anemia, and hyperchloremia. Brain magnetic resonance imaging (MRI) revealed definite cerebellar atrophy. We should consider the possibility of chronic BVU intoxication in peculiar neurological cases like ours.

Key words: bromisovalum, non-prescription drugs, movement disorders, hyperreflexia, cerebellar atrophy

Introduction

Bromvalerylurea (BVU = bromisovalum) is a kind of organic bromide belonging to the monoureide family. Inorganic and organic bromides, the latter being practically only BVU in medicine (1, 2), are known to cause acute and chronic intoxication. Respective poisoning symptoms due to these two compounds are said to differ in frequency and severity (3, 4).

BVU per se used to be widely used to treat insomnia and for sedation, but it is likely that its consumption in the world is tending to decrease because of the acute and chronic intoxication (5). Nevertheless, since nonsteroidal anti-inflammatory drugs (NSAID) containing BVU are available without prescription in Japan, we still occasionally encounter cases of chronic intoxication by BVU included in such NSAID (1, 5–11).

Acute BVU intoxication is usually associated with suicide attempts, and includes consciousness disturbance and respiratory failure (12). Meanwhile, chronic BVU intoxication, which is usually due to its abuse, involves various neurological symptoms and signs including tremor, cerebellar ataxia, pyramidal signs, ophthalmoplegia, peripheral neuropathy and autonomic dysfunction (11, 12).

We recently encountered a patient with chronic BVU intoxication presenting cerebellar ataxia, pyramidal signs and a dystonic posture of the neck. To our knowledge, this is the first case of chronic BVU intoxication showing a dystonic posture. In this report we emphasize that we should be aware of chronic BVU intoxication in cases of NSAID abuse which exhibit neurological features, as in our case.

Case Report

A 32-year-old housewife was admitted to our hospital because of gait disturbance at the beginning of October, 1996. After she had a fever of 38°C at the beginning of September 1996, she noticed tremor of the upper and lower extremities and the neck, gait disturbance, dysarthria, and nuchal myalgia. Neurological examination on the first admission revealed slurred speech, tremor of all the extremities, an ataxic gait, truncal titubation, diffuse hyperreflexia, bilateral ankle clonus, spasticity of the lower extremities, and bilateral Babinski signs. She had no history of alcohol abuse. We diagnosed her as having viral cerebellitis at that time. Since her symptoms had gradually improved within a month without any treatment, we decided to...
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follow her at our out-patient department.

After discharge, her gait disturbance gradually worsened again and she began to experience back myalgia. She was re-admitted to our hospital in March 1997, when we became aware of her Nalon-Ace® abuse for the first time. She had experienced chronic and intractable headaches at age 14, but never had received prescribed drugs including flunaridine. She had tried many over-the-counter (OTC) drugs on her own. At age 26 she noticed that Nalon-Ace® relieved her habitual headache, and she used to take about 24 tablets of the drug (2,400 mg of BVU) each month. When she was 28 years old (1992), she was taking about 48 tablets of the same drug a month (4,800 mg of BVU). Neurological re-examination in March 1997, revealed a dystonic posture of the neck (she protruded her head anteriorly) in addition to slurred and explosive speech, limb and truncal ataxia, tremor, hyperreflexia, ankle clonus, spasticity of the lower extremities, and a Babinski sign on the right side.

Laboratory tests on the second admission revealed iron deficiency anemia with low hemoglobin (10.8 g/dl) and serum iron (27 µg/dl; normal, 70–130) levels, and elevation of unsaturated iron binding capacity (348 µg/dl; normal, 150–320). Serum chloride iron was as high as 115 mEq/l (normal 96–108). Liver function tests were normal. Although the antibody titer of Influenza B was as high as x4,096 (hemagglutinin inhibition), there was no difference in the antibody titer between the first and second admission. There were no remarkable findings regarding the cerebrospinal fluid, endocrinological data, or serum vitamins. Molecular testing of the genes responsible for spinocerebellar ataxia type 1 (SCA1), spinocerebellar ataxia type 2 (SCA2), Machado-Joseph disease, spinocerebellar ataxia type 6 (SCA6), and dentatorubralpallidoluysian atrophy (DRPLA) revealed no expansion of the CAG repeat units. The serum concentrations of organic bromide were found to be high retrospectively (16 mg/dl: October 9, 1996; 26 mg/dl: May 1, 1997; 26 mg/dl: May 30, 1997; Normal <0.5). Head magnetic resonance imaging (MRI) revealed definite cerebellar atrophy, especially in the upper hemisphere (Fig. 1).

Discontinuance of Nalon-Ace® led to improvement of the spasticity of the lower extremities and the ataxic gait (Fig. 2).

Discussion

The diagnosis of this case was chronic BVU intoxication, based on the following findings: 1) a distinct history of abuse of Nalon-Ace®, which contains BVU, 2) elevated serum BVU concentrations, 3) relief of symptoms after cessation of Nalon-Ace® ingestion, 4) worsened symptoms on its retrial, and 5) pseudo-hyperchloremia. Although chronic BVU intoxication usually becomes apparent at a serum BVU level of 50–80 mg/dl (1, 5), the present case developed neurological symptoms with relatively low serum concentrations of BVU (16–26 mg/dl). This might be due to different individual sensitivities to BVU.

The clinical features of chronic BVU intoxication comprise various combinations of ocular symptoms, pyramidal signs, tremor, ataxia, and autonomic nervous dysfunction (13). In particular, cerebellar ataxia is a common clinical feature of the intoxication (3, 4). Since previous reports on this condition did

Figure 1. Brain MRI (T1-weighted). A: sagittal section with Gadolinium enhancement. B: axial section. Brain MRI revealed definite cerebellar atrophy.
not mention dystonia, the dystonic posture of the neck in our patient is noteworthy. This finding suggests that BVU affects not only the cerebellar but also the extrapyramidal system.

Brain MRI in our case revealed cerebellar atrophy, which was intensified in the upper portions of the vermis and hemispheres, which resembles that in several cases of chronic BVU intoxication (9, 11, 14). Miyama reported that cerebellar Purkinje cells were lost in such cases (7). Since this pattern of cerebellar atrophy in chronic BVU intoxication resembles those in chronic alcoholism and phenytoin intoxication (9), the mechanism underlying the cerebellar atrophy might be common in these conditions.

The non-neurologic manifestations of chronic BVU intoxication include skin lesions like acneiform eruptions, anemia, and body weight loss due to unknown mechanisms (2, 4, 12, 13). We observed iron deficiency anemia in this case too, but it remains undetermined whether or not iron deficiency is a common mechanism of anemia seen in BVU intoxication; Arai et al reported anemia possibly due to folic acid deficiency in a case of BVU intoxication (11). The present case exhibited microcytic and hypochromic anemia, and normal folic acid and vitamin B12 levels, which thus probably rules out folic acid deficiency as the cause of the anemia. Apparent hyperchloremia is usually noted in BVU poisoning because bromides cannot be distinguished from chlorides, and are quantitated as chlorides with conventional measurement methods (2). In our case, the presence of pseudohyperchloremia was a key to the accurate diagnosis of BVU poisoning, as in some previous reports (2, 8, 15).

Although there have been many case reports of acute BVU intoxication due to its use in suicide attempts in Japan, our intensive literature search revealed only 12 cases of chronic BVU intoxication (5–11, 15). However, chronic BVU intoxication is speculated to occur more frequently because many people are likely to habitually use OTC NSAID including BVU in Japan. In cases showing cerebellar ataxia, pyramidal signs and a dystonic posture, we should be aware of chronic BVU intoxication and should check the history of such NSAID abuse. Furthermore, we should recognize that there are a number of other drugs that contain BVU and thus can cause such intoxication (2). Moreover, it may be necessary to advise patients on the proper usage of OTC drugs.

References
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