



Diffusion-Weighted Imaging for Detecting Glufosinate Ammonium Intoxication: A Case Report

글루포시네이트 암모늄 중독 환자의 확산자기공명영상 소견: 증례 보고

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Glufosinate ammonium-containing herbicides are non-selective herbicides, used worldwide. With the increasing use of glufosinate ammonium-containing herbicides, cases of acute intoxication in suicide attempts have also increased. Herein, we report a case of a patient presenting cytotoxic edema in the posterior limbs of the bilateral internal capsules, bilateral middle cerebellar peduncles, and splenium of the corpus callosum on the brain diffusion-weighted MRI after glufosinate ammonium intoxication.

Index terms Glufosinate Ammonium; Magnetic Resonance Imaging; Herbicides; Poisoning

INTRODUCTION

Glufosinate ammonium (GLA) is a commercial herbicide that is widely used globally. It inhibits glutamine synthetase, which plays an important role in ammonia catabolism in plants, resulting in ammonia accumulation and eventual toxicity in the plants. The first report of GLA intoxication was in Japan in 1989, and since then, cases of GLA intoxication have been reported steadily (1). Most glufosinate intoxication cases were associated with the ingestion of BASTA (Bayer, Leverkusen, Germany), a herbicide containing GLA (18.5%) and an anionic surfactant, polyoxyethylene alkyl ether sulfate (AES) (30%) (2). In the early stage, gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain occur due to mucosal irritation by surfactants, followed by respiratory depression, fever, and intractable hypoten-

sion. Unlike other herbicides, GLA can cause neurological symptoms such as altered mental status, convulsions, and memory loss. However, the mechanism that causes these symptoms has not yet been elucidated (1). The mortality rate of GLA poisoning has been reported to be about 26% (3), with the cause of death thought to be related to circulatory system problems. Particularly, a large amount of surfactant in GLA-containing herbicide may lead to death from cardiac insufficiency (1). Radiologically, in the case of central nervous system (CNS) lesions, white matter ischemias, cytotoxic edema in the hippocampus, vasogenic edema in the striatum with hippocampal lesions, and reversible splenial lesions of the corpus callosum have been reported (1, 2, 4, 5). Here, we report a case of GLA intoxication in a patient who presented with cytotoxic edema in the posterior limbs of the bilateral internal capsules, bilateral middle cerebellar peduncles, and splenium of the corpus callosum on brain diffusion-weighted imaging (DWI) MRI.

CASE REPORT

A 76-year-old female was transferred to the emergency department in a semi-coma mental state at 2 hours after the ingestion of BASTA. The patient was found lying down by her guardian, and the exact ingested amount could not be estimated because the content in the bottle was spilled. The patient had a medical history of diabetes and hypertension, which was controlled by oral pills. Gastric lavage was performed in the emergency room, and immediate endotracheal intubation and assisted ventilation were initiated for airway maintenance. The patient's initial vital signs were unstable (blood pressure, 258/153 mm Hg; heart rate, 137 beats per minute). At 2 hours after admission, hypotension developed (blood pressure, 90/46 mm Hg), and the blood pressure gradually increased after administration of norepinephrine. Arterial blood gas analysis revealed metabolic acidosis (pH, 7.15; PCO₂, 39 mm Hg; PO₂, 288 mm Hg; HCO₃, 14 mmol/L; base excess, -15 mmol/L). Initial blood ammonia level was 295 µg/dL, which gradually decreased after admission and normalized on the 13th day of admission. Baseline chest X-ray and electrocardiogram showed no abnormalities. On the fourth day of admission, atrial fibrillation developed, and the patient was treated with antiarrhythmic medication. On the 11th day of admission, chest X-ray detected increased opacities in both the lungs, which was suggestive of ventilator-associated pneumonia, and treatment was initiated with antibiotics.

On the 13th day of admission, brain DW-MRI was performed. High signal intensities were observed on DWI in the posterior limbs of the bilateral internal capsules, bilateral middle cerebellar peduncles, and splenium of the corpus callosum (Fig. 1A, B). These lesions had low apparent diffusion coefficient (ADC) values, indicating cytotoxic edema (Fig. 1C, D). The patient remained unconscious with a semi-coma mental status until 1 month after admission. The patient's guardian did not want any further evaluation or treatment, and the patient was transferred to a nursing hospital for conservative care.

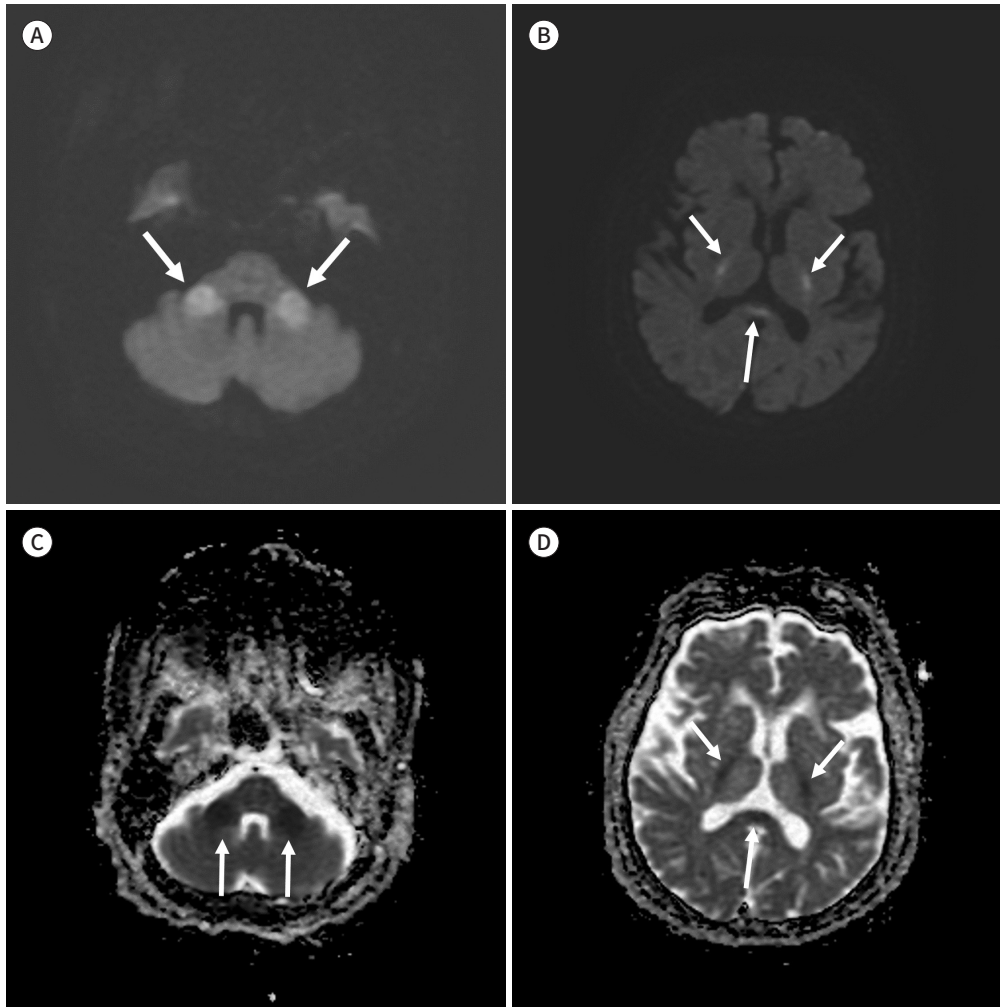
This case report was approved by the local Institutional Review Board, and the requirement for written informed consent was waived (IRB No. 2021-08-024).

Fig. 1. Diffusion-weighted imaging and ADC mapping of a 76-year-old female on day 13 following glufosinate ammonium intoxication.

A, B. High signal intensities (arrows) are demonstrated in the bilateral middle cerebellar peduncles (**A**) and posterior limbs of the bilateral internal capsules and splenium of corpus callosum (**B**).

C, D. Low ADC values (arrows) are observed in the bilateral middle cerebellar peduncles (**C**) and posterior limbs of the bilateral internal capsules and splenium of corpus callosum (**D**), suggesting cytotoxic edema.

ADC = apparent diffusion coefficient



DISCUSSION

GLA-containing herbicide is a non-selective herbicide that is composed of 18.5% GLA and 30% AES as an anionic surfactant (2). Clinical manifestations associated with GLA-containing herbicide intoxication are classified into two categories: early gastrointestinal symptoms and late neurological symptoms. Gastrointestinal symptoms related to mucosal irritation are caused by surfactants; however, the cause of late neurological symptoms such as convulsions, loss of consciousness, or memory loss is unclear (1). Koyama suggested that the cause of the neurological symptoms after GLA-containing herbicide poisoning is mainly due to the effects of GLA (6).

Glufosinate is a structural analogue of glutamate that can directly stimulate glutamate re-

ceptors, which induce excitotoxic injury (1). A few brain imaging studies on GLA-containing herbicide intoxication have been conducted, and most of them found abnormal signal intensities in the hippocampus (4, 7). Neurons in the hippocampus act via glutamate receptors. Moreover, glutamate functions as the main neurotransmitter in this brain area. Therefore, excessive stimulation of glutamate receptors, especially N-methyl-D-aspartate-type glutamate receptors, might cause hippocampal injury (4, 7). Other studies on GLA-containing herbicide intoxication have reported brain lesions at different sites with or without hippocampal involvement. Lee et al. (2) reported a case of vasogenic edema in the striatum accompanied with cytotoxic edema in the hippocampus after ingestion of GLA-containing herbicide. They suggested that the surfactant-induced vascular autoregulatory dysfunction and additional vasodilative effects might be the mechanism of vasogenic edema in the striatum. Jeong et al. (5) reported a case of reversible splenic lesions following GLA-containing herbicide intoxication. They indicated three different mechanisms of GLA-induced splenic lesions. First, GLA increases the extracellular glutamate levels, which directly cause excitotoxic effects on the neurons by inhibiting glutamine synthetase. Second, GLA directly stimulates the glutamate receptor since it is a structural analogue of glutamate. Third, hyperammonemia associated with GLA-containing herbicide intoxication causes swelling of astrocytes, the cells that have abundant glutamate receptors and transporters, thereby preventing acute-phase neuronal injury from the reuptake of glutamate, resulting in the reversibility of the lesions. Watanabe and Sano (1) reported a case of marginally high signal intensity lesions in the paraventricular white matter area on axial T2-weighted imaging following GLA-containing herbicide intoxication. In this study, ischemia of the white matter was associated with circulatory imbalance during the acute phase of intoxication.

The present case had high signal intensities in the posterior limbs of the bilateral internal capsules, bilateral middle cerebellar peduncles, and splenium of the corpus callosum on DW-MRI and low signal intensities on the ADC map, indicating cytotoxic edema. To the best of our knowledge, this is the second report of GLA-containing herbicide intoxication, showing abnormal signal intensities in these areas. Kim et al. (8) reported the first case that showed high signal intensities in the splenium of corpus callosum, bilateral posterior limbs of internal capsule, bilateral cerebellar peduncles and bilateral cerebral peduncles of midbrain as well as bilateral hippocampi on DWI and fluid-attenuated inversion recovery (FLAIR) images. This report is very similar with our case report, only difference is whether involvement of bilateral hippocampi and bilateral cerebral peduncles of midbrain. Authors indicated that this suggests that brain regions susceptible to injury from GLA-containing herbicide intoxication may not only include the hippocampus but also the white matter tracts, including the posterior limbs of the internal capsule, middle cerebellar peduncle, and splenium (8). Although the exact cause of these lesions was unclear, the cytotoxic edema in the white matter tracts after GLA-containing herbicide intoxication might have been associated with hypoxic brain injury from severe hypotension as well as direct excitotoxic injury induced by glufosinate, similar to that observed in other reported cases.

Differential diagnoses of the brain lesions in the posterior limbs of the bilateral internal capsules with symmetrical involvement of the bilateral middle cerebellar peduncles include heroin-induced leukoencephalopathy. Keogh et al. (9) reported cases of heroin inhalation-in-

duced leukoencephalopathy, which demonstrated bilateral symmetric high signal intensity in the middle cerebellar peduncles and pons on T2-weighted and FLAIR imaging with symmetric involvement of the cerebellar white matter and posterior limbs of the internal capsule and without the involvement of the anterior limb. The Classic MR findings of heroin inhalation-induced leukoencephalopathy include symmetric high signal on T2-weighted and FLAIR sequences in the cerebellar and posterior cerebral white matter, posterior limb of the internal capsule (9). The pathologic findings are symmetric spongiform degeneration of the white matter tracts in these areas. Although exact etiology and pathogenesis has not yet been found, it is thought that unknown chemicals produced by heating the drug on aluminium foil and mitochondrial toxicity are related in pathogenesis (9). It may be difficult to differentiate GLA-containing herbicide induced brain lesions from heroin inhalation-induced leukoencephalopathy when only the white matter tract is involved without affecting the hippocampus as in our case.

The anionic surfactant, AES, in GLA-containing herbicide, induces nitric oxide production and dilation of blood vessels, causing hypotension and cardiac suppressive effects in extremely severe intoxication (10). In line with this effect, the present patient presented with hypotension at 2 hours after admission. Furthermore, the surfactant in GLA-containing herbicide increases the permeability of the blood-brain barrier, facilitating CNS entry and toxicity enhancement of glufosinate (1).

This study has a limitation in that the patient was continuously unconscious even after 1 month of admission, and no additional follow-up brain imaging was conducted. Thus, it was not possible to correlate the brain lesions with the patient's neurological symptoms. Furthermore, the patient showed hyperammonemia until 13th day of her admission, and DW-MRI was performed after that, it is possible that the brain lesions were secondary change due to metabolic derangement such as hyperammonemia rather than GLA-containing herbicide intoxication, despite hyperammonemic encephalopathy mostly affect cerebral cortex including insula and cingulate gyrus.

In conclusion, brain lesions due to GLA-containing herbicide intoxication are not restricted to the hippocampus, but they also include the white matter tracts of the posterior limbs of the bilateral internal capsules, bilateral middle cerebellar peduncles, and splenium of the corpus callosum, which showed cytotoxic edema on DWI.

Author Contributions

Conceptualization, P.N.H.; supervision, P.N.H.; visualization, P.N.H.; writing—original draft, K.H.Y.; and writing—review & editing, P.N.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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글루포시네이트 암모늄 중독 환자의 확산자기공명영상 소견: 증례 보고

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글루포시네이트 암모늄은 세계적으로 널리 사용되는 제초제로서, 글루포시네이트 암모늄을 함유하는 제초제의 사용이 증가하면서 그에 따른 급성중독 사례도 증가하고 있는 추세이다. 이에 저자들은 글루포시네이트 암모늄 중독 후 발견되는 뇌 확산자기공명영상 소견에 대해 보고하고자 한다. 증례에서 환자는 양측 속섬유막, 중간소뇌다리, 뇌량팽대에서 세포독성부종 소견을 보였다.

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