A case of glyphosate encephalopathy presented with retrograde amnesia and an increase of blood flow in the medial temporal lobes on the arterial spin labeling images.

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Abstract

***Background*: Suicide attempts with glyphosate-based herbicides are not rare in rural areas in Japan. There are some reports on glyphosate encephalopathy, however, the detailed features of the clinical course are still unclear.**

***Case:* A female case in her early 70s was hospitalized after ingesting a glyphosate-based herbicide. On the fifth day after admission, she developed confusion and cognitive impairment including retrograde amnesia, even though her general condition was improved. An increase of blood flow in the bilateral medial temporal lobes was observed on the arterial spin labeling (ASL) of magnetic resonance image (MRI). The electroencephalogram (EEG) showed paroxysmal activities centered on the right temporal electrodes, suggesting pathological lesions with abnormal neuronal activity or glial activity in the medial temporal lobes. After sodium valproate and olanzapine were administered, her psychiatric symptoms and cognitive impairment were improved and the findings on the MRI and the EEG were rectified, although retrograde amnesia remained.**

***Conclusions:* Patients who ingested glyphosate would need careful management considering the subsequent glyphosate encephalopathy with pathological lesions in the medial temporal lobes. The findings of ASL study and EEG were salient and may be useful for the early detection and management of encephalopathy.**

Key words: glyphosate encephalopathy, cognitive impairment, retrograde amnesia, medial temporal lobes, arterial spin labeling, electroencephalogram

Introduction

Glyphosate poisoning can be caused by deliberately or mistakenly ingesting a large volume of glyphosate-based herbicide. Especially in rural areas in Japan, suicide attempts with glyphosate-based herbicides are not rare [1]. There are some reports on glyphosate encephalopathy [2-5] which suggests involvement of pathological lesions of medial temporal lobes and epileptic activity. However, the details of clinical course of deterioration in mental status are not elucidated fully.

Glyphosate-based herbicides are comprised of glyphosate and surfactants. Glyphosate exhibits acidity and induces acidosis, renal injury, and hepatic injury while surfactants augment the toxicity of

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glyphosate and induce gastrointestinal corrosive action, mucosal damage, and circulatory/respiratory failure [6-9]. Glyphosate is also reported to act as an analogue of glycine/glutamate in the nervous system and exhibit glutamate excitotoxicity, oxidative stress and neuroinflammation [10, 11].

Here, we report a case of glyphosate encephalopathy who presented with retrograde amnesia with an increase of blood flow and paroxysmal waves on encephalogram in the medial temporal lobes, and discuss how to detect useful manifestations for early diagnosis and better management of glyphosate encephalopathy.

The patient was treated at Kindai University Nara Hospital. She and her family gave permission for the study and its publication, and the patient's privacy was duly protected. This study was approved by the Ethics Committee at Kindai University Nara Hospital and was conducted in accordance with the Helsinki Declaration. All the authors have no conflicts of interest concerning this study.

Case

A woman in her early 70s repeatedly had depressive episodes and suicide ideation but had never seen a psychiatrist. She ingested 50-100ml of a herbicide "Round-up Max Load" containing 48% glyphosate potassium (Glycine, N-(phosphonomethyl)-, potassium) salt, 52.0% water and surfactant. After four hours, her family found her having nausea, vomiting, and dizziness. She was rushed to the emergency room of our hospital after another hour. Upon arrival at our hospital, vomiting, hypotension, acidosis, renal failure, and hyperkalemia were observed. Her consciousness and cognitive function were not affected. She was treated with gastric lavage, glucose-insulin-potassium therapy, intravenous administration of saline and sodium bicarbonate, spherical carbonaceous adsorbent, and laxative. Fortunately, vasopressor, hemodialysis, ventilator, or sedation were not necessitated. The symptoms were smoothly improved by the eighth day after admission.

Contrary to the improving general condition, cognitive impairment and confusion emerged on the fifth day and continued. Sudden changes in emotion, thinking and behavior, as well as inattention, impaired short memory, retrograde amnesia, and disorientation were observed. Neither of renal failure, electrolyte imbalance, nor dehydration recurred. Hepatic dysfunction, hyperammonemia, anemia, infection, respiratory failure, heart failure, hyper/hypoglycemia, hypothyroidism, vitamin B1 deficiency, or syphilis were not seen. She had neither history of substance abuse, chronic use of benzodiazepines, nor dementia. She had not developed motor symptoms.

The head magnetic resonance image (MRI) was performed on the eighth day. T2 fluid attenuated inversion recovery (T2 FLAIR) (Figure 1A), T2-weighed (T2W) (Figure 1B), T1-weighed (T1W) and diffusion weighted imaging (DWI) (not shown) of MRI did not suggest specific findings concerning the psychiatric symptoms except hippocampal sulcus remnant cysts, aging-related atrophy and white matter hyperintensity. However, the arterial spin labeling (ASL) displayed high-intensity signals in the bilateral medial temporal lobes, suggesting an increase of blood flow in the areas (Figure 1C). The electroencephalogram (EEG) showed paroxysmal waves on the right temporal (T4, T6), frontal (F4), and central (C4) electrodes (Figure 2), suggesting a risk of epilepsy. The result of a cerebrospinal fluid examination was in the normal range.

On the ninth day, she scored 5/30 on the Revised Hasegawa's Dementia Scale (HDS-R).

Based on previous reports [2-5], she was diagnosed with glyphosate encephalopathy, of which lesions were centered in the medial temporal lobes. The lesions suggested a possibility of abnormal neuronal or glial activity because increased blood flow was observed.

The risk of epilepsy and confusion had to be addressed. Therefore, 800 mg of sodium valproate and 7.5 mg of olanzapine per day were administered. The impairment of her emotion and attention was appeased and the HDS-R score was 13/30 on the 20th day. On the 33rd day, there were no obvious changes on T2 FLAIR images (Figure 3A and 3B). The high signals on ASL subsided (Figure 3C) and the findings of EEG were rectified. The HDS-R score was 21/30 on the 40th day and 26/30 on the 48th day, but retrograde amnesia remained.

Discussion

According to previous reports, glyphosate poisoning could lead to later emergence of encephalopathy [2-5]. In our case, it occurred on the fifth day, when the general condition was smoothly improving, which was not explicable by common delirium. Other potential etiology of cognitive and psychiatric dysfunction was excluded, and she was diagnosed as having glyphosate encephalopathy.

Previous reports [2,4,5] noted hyperintensity and swelling of the medial temporal lobes on T2 FLAIR

Figure 1A Figure 1B Figure 1C

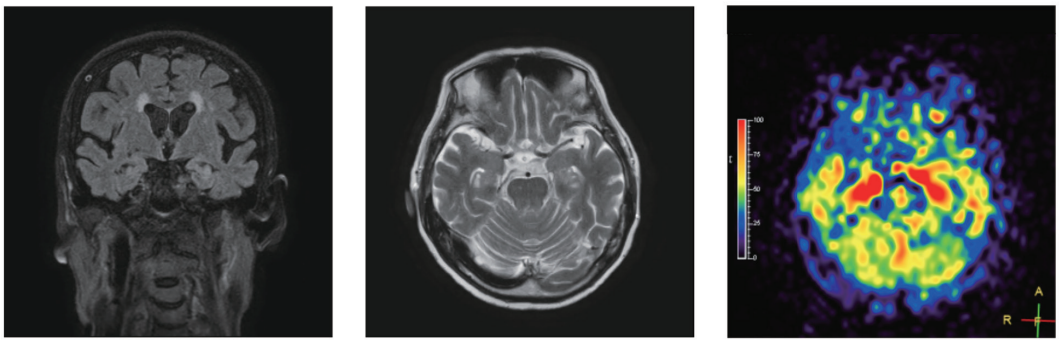

Figure 1. The findings of MRI and EEG on eighth day after admission.

Figure 1A: The T2 fluid attenuated inversion recovery (T2 FLAIR) image suggests aging-related atrophy and white matter hyperintensity which do not suggest explanation of the psychiatric symptoms.

Figure 1B: The T2-weighted image (T2W) showed no specific pathological findings except hippocampal sulcus remnant cysts in the medial temporal lobes.

Figure 1C: The arterial spin labeling (ASL) suggested an increase of blood flow in the bilateral medial temporal lobes.

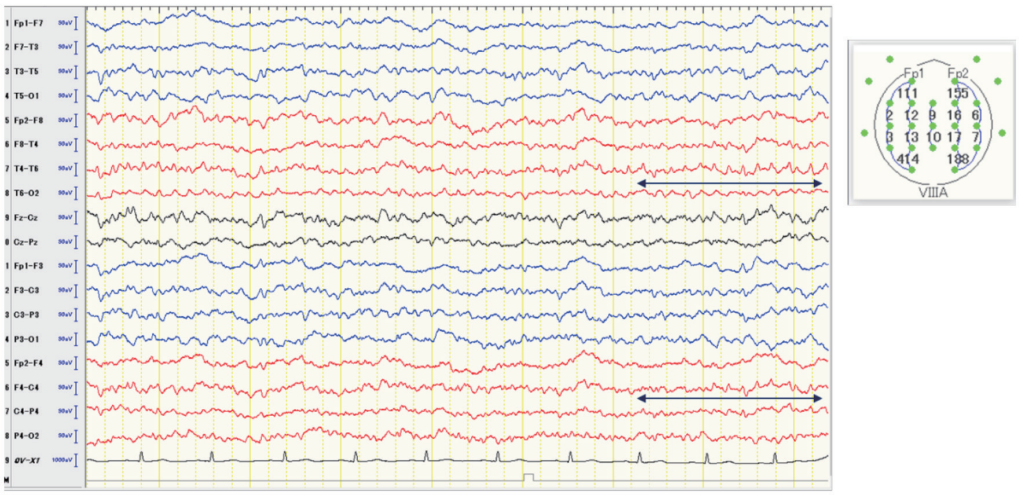

Figure 2. The electroencephalogram (EEG) on eighth day after admission. Paroxysmal waves on the right temporal (T4, T6), frontal (F4), and central (C4) electrodes were suggested as indicated by arrows.

Figure 3A Figure 3B Figure 3C

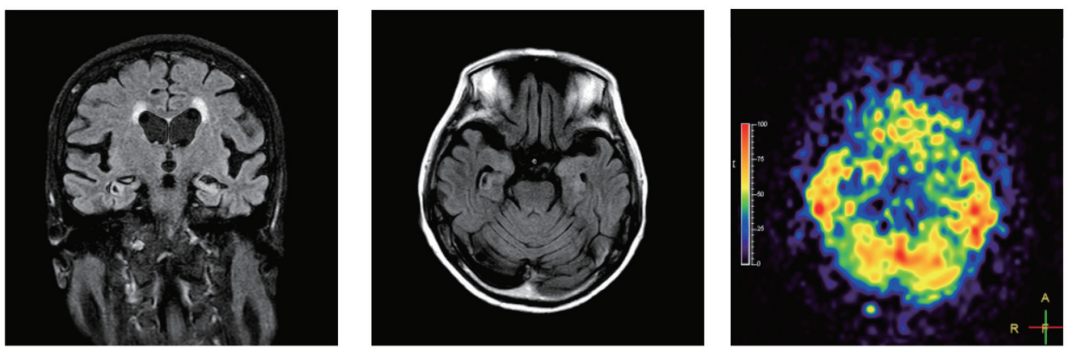

Figure 3. The findings of MRI on 33rd day after admission.

Figure 3A and 3B: The T2 FLAIR images showed no specific changes.

Figure 3C: The ASL study did not show high signals in the medial temporal lobes.

at the early stage and a decline in blood flow or metabolism on nuclear imaging (SPECT or ^{18}F-FDG-PET/CT) at the later stages (at least after a month). However, some patients may show hyperintense or large medial temporal lobes before the onset of the disease, which would make the diagnosis difficult. Declined blood flow and metabolism at the later stage cannot exclude neurodegenerative diseases other than glyphosate encephalopathy. In fact, one of the studies [2] reported hypersignals of medial temporal lobes on the apparent diffusion coefficient (ADC) map at the very early stage (day 2 of hospitalization) although the authors attributed it to the T2-shine-through effect. In our case, neither T2W nor DWI showed high signal intensity, suggesting high signals on the ASL depicted an increase of blood flow, not T2-shine-through effect in the medial temporal lobes.

The high ASL signals suggested pathological lesions at the early stage, such as excessive neuronal activity or glial activity. Excessive neuronal activity would need more energy and increase the blood flow [12]. Moreover, glutamate released from synapses would stimulate astrocytes to create an astrocytic calcium wave which reaches to the astrocytic endfoot encircling a blood vessel. Calcium ion in the astrocyte induces the production of arachidonic acid, which is metabolized into vasodilating prostaglandin by COX-1 [13,14]. Other molecules such as nitric oxide (NO) from microglia may also dilate blood vessels. Stress-related molecules such as extracellular adenosine triphosphate (ATP) or potassium ion may also induce vasodilatation [13]. Glyphosate is reported to mimic the function of glycine/glutamate in the nervous system and exhibit glutamate excitotoxicity, oxidative stress and neuroinflammation [10,11]. These detrimental mechanisms may affect the result of ASL imaging and may cause neurodegenerative changes. Glycine/glutamate-like action of glyphosate may induce paroxysmal neuronal activities on the EEG. Paroxysmal waves centered on the right temporal electrodes were suggested on the EEG when the ASL displayed hyperintensity in the medial temporal lobes. These findings, especially the ASL study, were salient at the early stage of encephalopathy, which may be useful for the early diagnosis and management of the encephalopathy.

The cognitive impairment and psychiatric symptoms were improved and kept stable thereafter. However, retrograde amnesia remained, presumably because organic changes occurred in the medial frontal lobes, which were not detectable on T1W/T2W, T2 FLAIR, or DWI of MRI. The result of ASL study was also in the normal range on the 33rd day. Diffusion tensor imaging (DTI) or magnetic resonance spectroscopy (MRS) might have been useful to investigate the pathological changes.

Conclusion

Patients who ingested glyphosate should be carefully treated considering the subsequent glyphosate encephalopathy. Adding ASL when performing MRI and EEG would be useful for early diagnosis and management of encephalopathy. More research will be needed.

Acknowledgements

None.

Conflict of Interest

None.

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