Survivors from β-fluoroethyl acetate poisoning show a selective cerebellar syndrome

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ABSTRACT

Aim/background: β-Fluoroethyl acetate (FEA), a derivative of sodium fluoroacetate (Compound 1080, FA), is one of the high-potency toxic chemicals, and it has been used against rats and wild animals. Human casualties from FA or FEA poisoning, accidental or suicidal, have been reported. Survivors of the poisoning are extremely rare. The objective of this study is to present survivors of FEA poisoning.

Method: Data on the survivors were collected at the Department of Neurology over the past 20 years. Reviews of the medical record and brain imaging were performed.

Results: A total of 10 survivors of FEA poisoning were found. All of the cases were suicide attempts. The amount of FEA ingested varied from 600 to 1800 mg with a mean of 1200 mg, which is close to the lethal dose of FEA. Immediately after ingestion, all of the patients had an altered mental status. On awakening, all of the patients had severe cerebellar dysfunction, such as ataxic gait, dysarthria and intention tremor. The cerebellar dysfunction usually improved gradually over the years after the event, but this improvement eventually plateaued, resulting in residual and persistent cerebellar dysfunction. Serial imaging showed swelling in the posterior fossa during the acute phase and progressive cerebellar atrophy on follow-up.

Conclusion: In summary, FEA poisoning causes a selective cerebellar syndrome in its survivors. The pathomechanism underlying the selective cerebellar toxicity of FEA remains to be elucidated. The selective involvement of the cerebellum might provide a useful model for cerebellar degeneration.

In 1992, one of the authors reported a unique and stereotypical clinical syndrome, selective cerebellar syndrome, following β-fluoroethyl acetate (ethyl fluoroacetate, FEA) poisoning.[1] FEA is an ethyl ester of sodium fluoroacetate (Compound 1080, FA), which is one of the high-potency toxic chemicals.[2] FA was introduced as a rodenticide. Even though it was very effective in controlling pests, its use became limited only to licensed personnel due to human fatalities and ecological concerns that the entire animal population of a poisoned area could be destroyed.[3] In the United States, Australia and New Zealand, FA is licensed for use against wild animals, such as coyotes, and it is deemed to be a potential chemical terrorism agent.[3 4] Its use was banned in Korea in 1966. However, its derivative FEA (Fratol) had been available to the general public as an effective pest control agent with less than optimal regulation until 2005. FA and its weaker version FEA are banned or severely restricted in most countries, and so cases of FA or FEA poisoning are very rare.[3] Survivors of FA or FEA poisoning are even rarer. Only 10 articles of survivors from FA intoxication have been published outside Korea.[5–14] Most of the reports in the literature are anecdotal reports of a single case.[5–10 14]

FA is converted to fluoroacetyl coenzyme A, and it combines with oxaloacetate to form fluorocitrate, which blocks aconitase in the Krebs cycle.[15–18] Therefore, it is an inhibitor of cellular respiration like cyanide, carbon monoxide (CO) and 3-nitropropionic acid (3-NPA). In contrast to the basal ganglionic syndrome seen in cyanide, CO and 3-NPA poisoning,[19–23] the FEA poisoning survivors discussed in our previous study presented with cerebellar syndromes.[1] A preliminary report of seven cases has been published in Korea.[1]

Aside from our previous report,[1] only eight communications of neurological complications of FA poisoning exist.[5–7 9 10 12–14] Trabes *et al* described a patient with cerebellar dysfunction in whom diffuse atrophy involving the cerebral and cerebellar cortices was seen on CT.[10] We attempted to construct an animal model of cerebellar degeneration using the toxin, but could not make much progress due to a lack of expertise in the pathology of FEA poisoning.[24] As FEA intoxication is rare and its survivors even rarer, we were only able to find three new cases of FEA survivors after 1992 (last case seen in 1995). All of the new cases had intoxication before 1982. Since it appears difficult to collect new cases, we wish to report these three cases in addition to the seven previously reported patients in order to draw the attention of the medical community to the selective cerebellar toxicity of FEA.

SUBJECTS AND METHODS

Between 1984 and 2007 (last case seen in 1995), 10 patients presented to the Department of Neurology, Seoul National University Hospital (a nationwide referral hospital) with cerebellar dysfunction of acute onset after Fratol poisoning. Six patients were seen years after the initial poisoning, but four patients were followed from the early stage. The six patients who presented years after the poisoning visited our hospital to search for a new remedy. Patient medical records were obtained, and the information in the medical histories was discussed with the patients. Information regarding acute poisoning, amount ingested, initial condition and management, and later development of neurological problems and chronological follow-up was obtained. The amount ingested by each patient was estimated based on the medical history and the discussion with patients. Fratol was manufactured by a

Korean company until 2005, and it came in a 30 ml bottle of a 2% solution, containing 600 mg of FEA. The institutional review board of the Seoul National University Hospital approved the study and presentation of the results.

RESULTS

Clinical information

All poisoning was the result of suicide attempts. The initial management of the acute poisoning was mostly done by other hospitals in the local area. The patients received supportive care for intoxication. Some were treated with monoacetin (glyceryl monoacetate), which stops the conversion of FA by intracellular liberation of acetate.[25] None of the patients suffered from hypoxaemia, seizures or other metabolic derangements during the acute stage. Probable cerebellar dysfunction was most prominent immediately upon recovery from the coma. All of the patients were shaky and unable to sit or stand. The patients were so tremulous that they were unable to feed themselves, and they were hard to understand due to dysarthria. The neurological deficits improved over a period of months to several years but eventually plateaued. Most of the patients visited our hospital due to unsteady gait and dysarthria. On the examination done at the presentation to our hospital, the most prominent neurological abnormalities were gait ataxia and dysarthria. Limb ataxia tended to be moderate. Nystagmus was rare and mild if present. No bradykinesia or rigidity was found. Spasticity could be seen during the acute phase and immediately after awakening but regressed during the follow-up period. The patients tended to be hypotonic. Upon recovery from acute poisoning, the patients were able to return to work or school in spite of substantial motor disability. Cognitive deterioration was not a factor in disability by history. The Mini-Mental State Examinations were normal in all cases when residual cerebellar dysfunction persisted years after recovery from the initial state of altered mentality.

Patient 4

Patient 4 was a 34-year-old woman, who was comatose for 7 days after taking 1200 mg of FEA. On awakening, her speech was unintelligible due to severe dysarthria, and she was unable to sit without assistance. On examination 1 month later, she had severe cerebellar dysarthria, mild dysphagia, marked intention tremor, hypotonia and increased deep tendon reflexes (DTR) with downgoing toes. She was unable to sit without assistance. Her eye movements were normal without nystagmus. Cognition was within normal limits. Three months later, she was able to sit without assistance, but she continued to have difficulty standing, even with assistance. She improved slowly and was able to walk a few steps with a side rail after 10 months. She continued to have dysarthria and dysphagia, even though her condition was much improved. Her limb ataxia was still moderately disabling. She currently has difficulty walking without support. CT performed 3 days after drug ingestion showed obliteration of the quadrigeminal and prepontine cisterns, suggesting cerebellar swelling (fig 1A). Another CT scan performed 6 months later showed widening of the cisterns and mild cerebellar atrophy (fig 1B). MRI performed 1 year later showed marked cerebellar atrophy, suspicious cortical atrophy and subcortical white matter lesions (fig 1C–F).

Patient 10

Patient 10 was a 45-year-old woman who visited our clinic because of a headache. On examination, she had mild cerebellar dysarthria and bilateral clumsiness on rapid alternating movements. She walked independently, but her tandem gait was mildly abnormal. Her eye movements were normal without nystagmus. Her cognition was within normal limits. MRI showed cerebellar atrophy (fig 2). She stated that she began to experience ataxia in her 20s, and it was stationary ever since. She was admitted for work-up of a cerebellar syndrome of unknown aetiology. One of the authors was presented with this patient as a case of cerebellar ataxia of unknown cause during resident teaching rounds. The author immediately recognised the characteristic course of dysarthria and ataxic gait, and challenged her history of drug intoxication, at which point the patient reluctantly acknowledged having a history of FEA poisoning. She had ingested 1200 mg of FEA in an attempt to commit suicide at the age of 25. She was comatose for 13 days. On awakening, she had severe dysarthria and an unsteady gait. She was unable to stand unassisted initially, but she improved gradually over the course of several years.

Neuroimaging

Four patients had serial CT or MRI scans, as they were followed from the early stage. The scans showed diffuse swelling of intracranial structures, especially the posterior fossa, during the first week (fig 1A). Cerebellar atrophy appeared during the recovery phase and progressed on follow-up scans (fig 1B–D). Cerebellar atrophy was prominent in the bilateral hemispheres as well as in the midline vermis (figs 1C,D, 2A,B). In contrast to the necrosis of the basal ganglia or diffuse leucoencephalopathy seen in CO poisoning (see supplementary fig 1),[19–21] cerebral hemispheric lesions were observed in just a single case (patient 4), in which mild cortical atrophy and subcortical white matter lesions were observed (fig 1E,F).

Clinical and radiological findings are summarised in table 1. Eight of the patients were women, and two were men. The amount of FEA ingested varied from 600 to 1800 mg, with a mean of 1200 mg, which is close to the lethal dose of FEA (about 10 times that of FA, which is 2–10 mg/kg in humans).[26] All of the patients experienced a decreased level of consciousness for more than 7 days (range 7 to 20 days with a mean of 12 days). The follow-up period ranged from 2 to 22 years. Patient 4 continued to have difficulty walking without assistance at the last follow-up, and patient 7 continued to be unable to walk with support, even 15 years after the poisoning.

DISCUSSION

In this report of our 20-year experience with FEA poisoning, we indicate that a selective cerebellar syndrome appears to be a unique neurological syndrome caused by FEA intoxication. During the study period, we did not see any other neurological syndrome resulting from FEA poisoning. Mild cortical atrophy and subcortical white matter lesions were found on MRI in only one case (patient 4), but no relevant deficits were manifest.

After reviewing the patient histories and follow-up examinations, we were able to divide the clinical course of FEA poisoning into three phases: the acute phase, when patients suffer from stupor or coma most likely due to the acute toxicity of FEA; the recovery phase, when patients wake up from the initial state of altered mentality and show signs and symptoms of cerebellar dysfunction with partial resolution over months to several years; and finally the chronic phase in which the patients are left with residual and persistent cerebellar dysfunction.

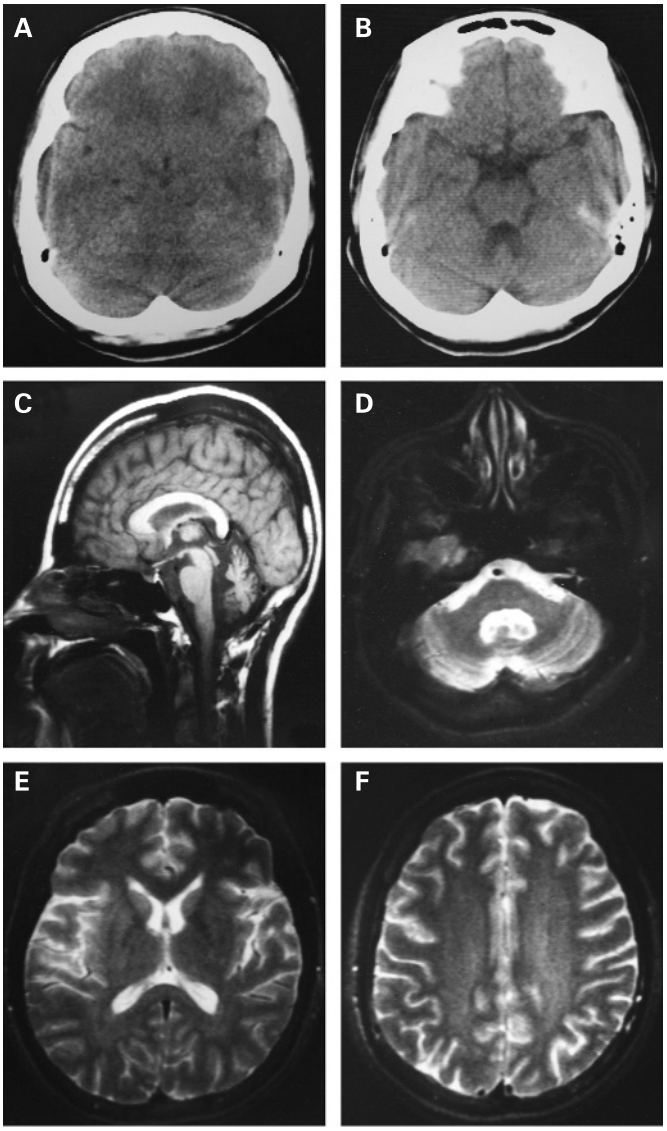

Figure 1 Representative CT and MRI of patient 4. (A) CT image acquired 3 days after intoxication showing obliteration of the fourth ventricle and sulcal marking in the posterior fossa suggesting swelling of intracranial structures. (B) CT image taken at 6 months showing widening of the cisterns and mild cerebellar atrophy. (C, D) T_1-weighted sagittal MRI (TR = 500, TE = 30) and T_2-weighted axial image (TR = 2500, TE = 80) taken 1 year later reveal severe atrophy of the cerebellar vermis and hemispheres. (E, F) T_2-weighted axial images showing no abnormality in the basal ganglia. Cortical atrophy was very mild in comparison with the cerebellar atrophy. Diffuse subcortical white matter lesions were also found but are less prominent than those of CO poisoning (supplementary fig 1).

The pharmacological properties of FA have been studied extensively,[3 12 16 26–28] but literature on FEA per se is lacking. FEA is the ethyl ester form of FA, and its toxicity is believed to be the de-esterified metabolite, FA. This de-esterification step is thought to be related to the reduced toxicity of FEA. Gajdusek, Luther, Reigart and colleagues suggested that FA toxicity is mainly due to seizure and cardiac toxicity.[5 7] However, none of our patients suffered from seizure or cardiovascular compromise. The discrepancy between our findings and those of previous studies may be related to the lower toxicity of FEA than that of FA.

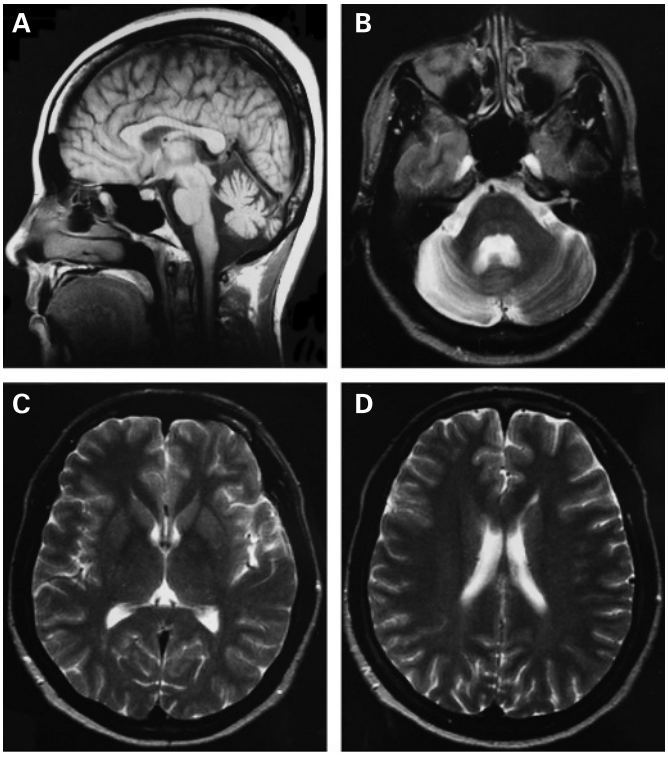

Figure 2 Representative MRI of patient 10. (A, B) T1-weighted sagittal MRI (TR = 600, TE = 15) and T2-weighted axial image (TR = 5000, TE = 22) taken 20 years after poisoning revealing a moderate degree of cerebellar atrophy. (C, D) Basal ganglia and cerebral hemispheres on T2-weighted axial images showing no abnormality (TR = 5000, TE = 90).

The selective dysfunction of the cerebellum in our patients is intriguing. FA is an inhibitor of cellular respiration like CO and cyanide. Thus, it is not surprising to find reports of global encephalopathy or seizure resulting from FA intoxication.[5–7 9 10 12–14] However, a patient reported by McTaggart and Pridmore experienced prolonged cardiac arrest for 10 min, which might have caused brain damage via a different mechanism than that of FA, which may have complicated the picture.[6 9] The patient showed dementia, epilepsy, tetraplegia, increased muscle tone with cogwheel rigidity and cortical blindness. Cerebellar dysfunction might have been overshadowed by spasticity and rigidity. Robinson and colleagues reported a case of intentional FA ingestion in United States.[14] The patient showed seizure and global encephalopathy, and received intubation and ventilator care. The patient improved over the course of 1 week and was discharged without neurological sequelae. The patient reported by Trabes *et al* attempted to commit suicide by ingesting FA.[10] She went through repeated seizures and was in a coma for more than 2 weeks, which resulted in severe cerebellar dysfunction, memory disturbances and depression. Her symptoms gradually improved, but her residual cerebellar ataxia persisted. In contrast to our patients, CT showed cerebral hemisphere atrophy in addition to cerebellar atrophy. The more widespread pathology in this case may be attributed to the fact that the toxicity of FA is greater than that of FEA. In patients 1 and 4, a slightly increased DTR or Babinski sign was observed, suggesting possible pyramidal involvement (see supplementary file). Postmortem examination of our patients would determine the distribution of histopathological lesions associated with FEA poisoning and pathological substrate of

Table 1 Summary of clinical and radiological findings

Patient no	1	2	3	4	5	6	7	8	9	10
Age*/gender	46/F	30/F	25/F	34/F	23/F	12/M	36/F	36/M	20/F	45/F
Amount ingested (mg)	1200	1800	1200	1200	600	1200	1200	Unknown	Unknown	600
Duration of altered mental status (days)	18	7	12	7	13	20	7	20	14	13
Time needed to walk unsupported	6 months	3 week	6 months	Unable†	6 months	12 months	Unable†	7 months	6 months	6 months
Initial evaluation‡	7 years	1 week	4 years	1 month	1 day	1 month	14 years	7 years	2 years	20 years
Follow-up	5 years	2 years	1 year	2 years	2 years	6 years	1 year	5 years	2 years	2 years
Dysarthria§	++	+	+++	++	++	++	+++	+	+	+
Ataxic gait§	+	+	+	+++	++	+	+++	+	+	+
Cerebellar atrophy	++	+	+++	++	++	++	++	+	++	++

*Ages of the patients at the time of presentation to our hospital.
†Unable: unable to walk without assistance (patient 4), or even with support (patient 7).
‡Initial evaluation means the interval between poisoning and presentation to our hospital.
§Dysarthria and ataxic gait are from the latest follow-up examination.
+, mild; ++, moderate; +++, severe.

the selective cerebellar syndrome. Magnetic resonance spectroscopy or positron emission tomography would be helpful to examine whether neuronal degeneration occurs outside the cerebellum.

Animal experiments have shown considerable species-specific variation in the clinical manifestations of FA poisoning.[25 26 29 30] Herbivores suffer primarily from cardiac toxicity, while carnivores tend to show central nervous system (CNS) involvement. Combined toxicity of FA in both the heart and CNS is characteristic of omnivorous animals, such as rhesus monkeys. Humans are similar to rhesus monkeys. It is important to address why the heart and brain are most vulnerable to FA. This selectivity might be explained by the difference in the activity of defluorination, which is the major detoxification pathway of FA.[26] The highest degree of defluorinating activity is found in the liver, followed by the kidney, lungs, heart and testicles.[26 31] There is no defluorinating activity in the brain. However, this lack of defluorinating activity in the brain does not explain the selective cerebellar dysfunction seen in FEA survivors. In addition to Krebs cycle blockage, hypocalcaemia by chelation and an increase in ammonia in brains of animals were proposed as the mechanisms of FA toxicity.[28] However, these mechanisms also do not explain the selectivity of cerebellar dysfunction.

Mettler and Sax reported that selective cerebellar degeneration was induced in the Rhesus monkey by intravenous infusion of azide.[32] They suggested that the selectivity could be explained by haemodynamics and vascular anatomy. However, the selectivity of other poisons that would cause similar haemodynamic changes, such as cyanide and CO, is quite different. Cyanide and azide inhibit the same enzyme, cytochrome C oxidase, but produce different pathologies in the basal ganglia or cerebellum, respectively.[20] 3-NPA is a suicide inhibitor of succinate dehydrogenase, another part of the electron transport chain. It is held responsible for mildewed sugarcane poisoning, causing basal ganglia necrosis and persistent dystonia among Chinese children.[22 23] FA and azide, which inhibit different enzymes, produce the same cerebellar toxicity. The inconsistency between the sites of enzyme inhibition and pathology is notable.

One interesting aspect of FA is that it is rather selective in inhibiting the metabolism and function of glial cells instead of neurons.[17 18 27 33] Thus, it does not decrease the overall consumption of oxygen because only the smaller energy cycle in the glia is blocked. Szerb and Issekutz demonstrated that FA inhibits glia from the inactivation of synaptically released glutamate in the rat hippocampus.[34] They suggested that the impaired reuptake of glutamate be related to the convulsive effect of FA. In the cerebellum, FA might hamper the modulation of excitatory inputs into cerebellar Purkinje cells by suppressing glial cells, thus causing excitotoxic injury to Purkinje cells.

Krebs cycle blockage by FA may increase the level of γ-aminobutyric acid (GABA) because its metabolism via transamination with α-oxoglutaric acid is inhibited due to the blockage of the Krebs cycle.[35 36] Patel and Koenig showed that the level of GABA rose by 82% in the fluorocitrate-treated cat spinal cord.[37] Though it has not yet been verified, the glial dysfunction induced by FA may hinder the uptake of released GABA and, in addition to blocking its metabolism, contribute to the increase in the levels of GABA. In the cerebellum, FA intoxication might increase the level of GABA, which is used as the main neurotransmitter throughout the complex neuronal network in the cerebellar cortex. Purkinje cells and inhibitory interneurons, the Golgi, basket and stellate cells use GABA. Axon collaterals from Purkinje cells exert inhibitory influences on Golgi cells, which subsequently inhibit granule cells. This disinhibition releases granule cells whose axons excite Purkinje cells. This feed-forward circuit might increase the excitotoxic burden to Purkinje cells and enhance the toxicity of FA. The enhancement of GABAergic neurotransmission during FA poisoning may explain the selective cerebellar syndrome seen in cases of FEA poisoning.

Cerebellar degeneration has been reported to be secondary to 5-fluorouracil chemotherapy.[38 39] The acute neurotoxic effects of 5-fluorouracil include encephalopathy, cerebellar dysfunction and, rarely, seizure.[39] Koenig and Patel reported the observation of neuron loss in the cerebellar dentate nucleus, granule cells and olivary nucleus during an autopsy of patients who died from acute 5-fluorouracil intoxication.[38] They proposed that FA is formed in the catabolism of 5-fluorouracil and exerts a deleterious influence.

In summary, we report a selective cerebellar syndrome occurring as a unique neurological syndrome in survivors of FEA intoxication. The selectivity of the cerebellum in FEA neurotoxicity has not been fully understood. A postmortem examination of our patients would be helpful for elucidating the pathological substrate of the selective cerebellar syndrome.

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Patient consent: Obtained.

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