

Impairment of the cortical GABAergic inhibitory system in catatonic stupor: a case report with neuroimaging

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ABSTRACT – We report the case of a 32-year-old patient who presented with catatonic stupor during the course of acute aseptic encephalitis involving the right frontotemporal area. Flumazenil-PET performed during the stupor indicated decreased benzodiazepine receptor binding in the right frontotemporal area where glucose metabolism was preserved as revealed by FDG-PET. An injection of diazepam immediately ameliorated catatonic symptoms and reduced widespread high amplitude slow EEG activities with right frontotemporal predominance. Compared with a SPECT study performed a week earlier, there was no abnormal right-sided anteriorly predominant cerebral hyperperfusion after injection of diazepam. While neither flumazenil- nor FDG-PET could be repeated, and with the caveat that generalized convulsions occurred initially and *epilepsia partialis continua* was present for two weeks starting on the 23rd day after illness onset, these findings suggest that in our case the presentation with catatonic stupor may be related to impairment of the cortical GABAergic inhibitory system.

Key words: catatonia, encephalitis, PET, SPECT, EEG

Catatonia is a neuropsychiatric syndrome presenting with dramatic changes in psychomotor activity, such as extreme negativism, peculiarities of voluntary movement, and echolalia or echopraxia. Catatonia is often comorbid with mood disorders, schizophrenia, and organic or non-organic brain disease. Diagnosis of symptomatic catatonic disorders is made based on the

DSM-IV criteria (American Psychiatric Association 2000). The neuropharmacological background of catatonic conditions has not been fully elucidated and it is clinically important as a differential diagnosis of epileptic seizures. We report the case of a patient with acute aseptic encephalitis manifesting catatonic stupor.

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Case report

A 32-year-old left-handed man acutely developed a severe non-throbbing headache. A few days later a generalized convulsion and consciousness disturbance occurred. Because the consciousness disturbance progressed within a week, he was transferred to our hospital for further examination and treatment. Neither the patient nor his family members had any neurological or psychiatric disorders in the past. The investigations, treatment, and clinical course of this patient are shown in *figure 1*.

General physical examination was unremarkable. The patient was in stupor, answering only 'Yes' to any questions. His eyes were open, but he did not respond even to noxious stimuli. He had spells of tongue protrusion (oral automatism) several times a day, each lasting 10 minutes. Nuchal stiffness was clearly recognized. Brain MRI showed T2 and FLAIR high intensity areas in the right insula and lateral temporal lobe involving the cortex and subcortical white matter (*figure 2A*); these areas of high intensity were not enhanced by gadolinium. A spinal tap revealed normal pressure (13 cmH₂O). The CSF showed moderate pleocytosis (34/mm³) with a predominance of mononuclear cells (89.2%), but glucose and protein levels

were normal. EEG showed poorly organized background activity consisting of a 10-Hz bioccipital rhythm and intermittent irregular slow activities localized in the right frontotemporal area. Fast activities were decreased in the right frontotemporal area as compared with the left. Herpes simplex encephalitis was suspected and acyclovir subsequently followed by vidarabine along with phenytoin was administered, but the patient's condition further deteriorated, and he developed automatisms in the left hand, which presented as a shaking-like movement that seemed to be repetitive and meaningless. He sometimes stared at one point without moving, and his body parts would remain fixed in the positions to which they were passively moved by an examiner (catalepsy). He was almost mute, but sometimes uttered nonsense words such as "bin, bin, bin" loudly (palilalia).

On the 18th hospital day (out of which 11 days in our hospital), 10 mg of diazepam was intravenously given while his EEG was continuously monitored. Before injection, EEG showed continuous, high amplitude 1-3-Hz semirhythmic activities diffusely, but predominantly, over the right frontocentral region throughout the recording (*figure 3A*). Immediately after the diazepam injection, the high amplitude slow activities markedly diminished,

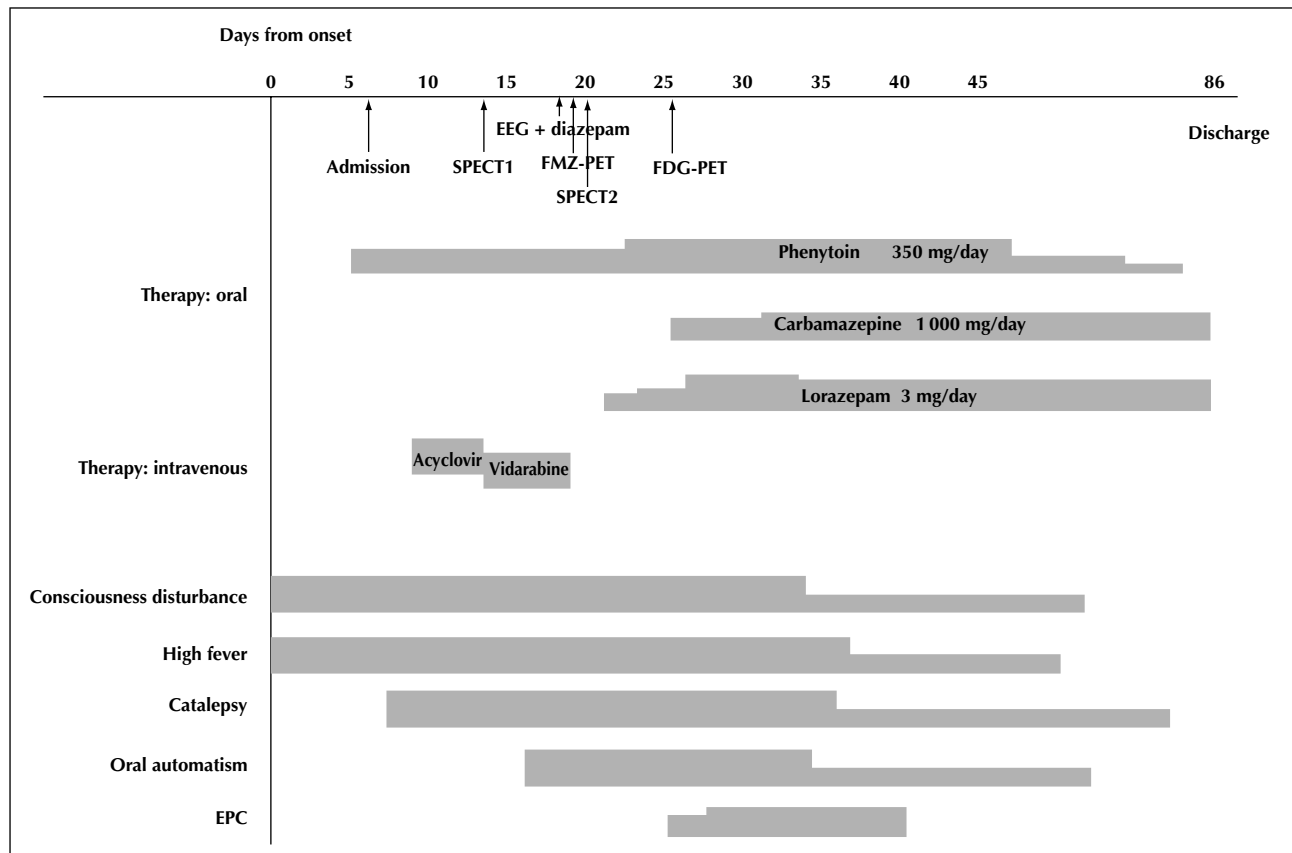


Figure 1. The investigations, treatment and clinical course of this patient.

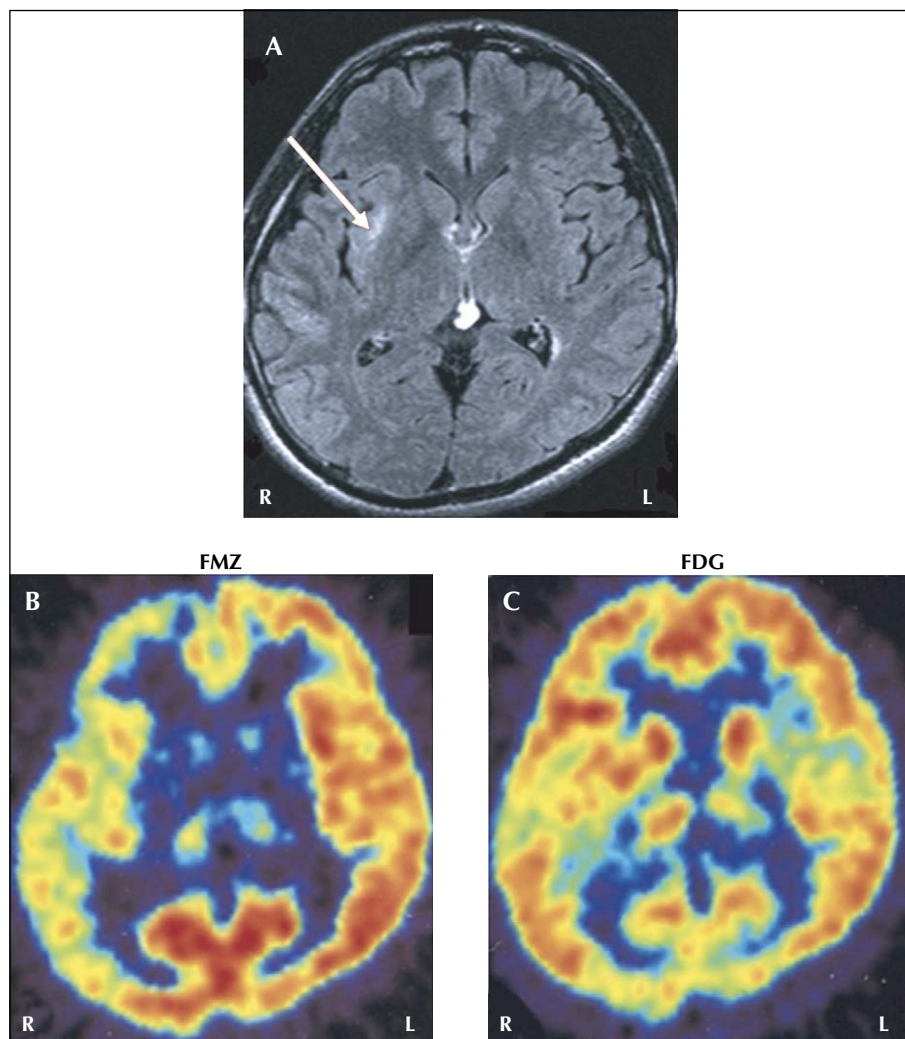


Figure 2. Brain MRI (A), flumazenil (FMZ) PET (B), and fluoro-deoxy-glucose (FDG) PET (C) obtained when the patient was in the state of catatonic stupor. The PET images are qualitative.

A) FLAIR image showing high intensity areas in the right temporal lobe and insula (arrow). B) FMZ binding was decreased in the right hemisphere. C) Glucose metabolism was normal in both hemispheres.

although low-voltage relatively rhythmic 1-Hz activity remained bilaterally (*figure 3B*). This dramatic change lasted for 20 minutes. The status of the patient also improved in parallel with EEG improvement. He began to move his extremities 20 seconds after the injection of diazepam, and started to speak although it was jargon. Furthermore, he could follow our instruction when we orally ordered him to raise his left hand. This status lasted for about 15 minutes. On the basis of these findings, we considered that the patient might have a symptomatic catatonic stupor; thus, we started oral administration of lorazepam from the 21st hospital day.

On the 23rd hospital day, he developed quasi-rhythmic movements in the left upper and lower limbs at an approximate rate of 1.5 Hz, which gradually spread to the right side of the body and lasted for 30 minutes.

These movements occurred intermittently for 13 days. EEG at that time showed a periodic pattern localized in the right frontocentral area (1.1-1.3 Hz) almost continuously, and EMG of the left brachioradialis at that time showed periodic brief contraction, suggesting *epilepsia partialis continua* (EPC). After the dose of anticonvulsants (phenytoin and carbamazepine) was increased, the patient's condition gradually improved, except that the EPC lasted for 13 days. He was discharged on the 86th hospital day and returned to his normal daily activity. He was able to resume his previous employment without obvious neuropsychological problems at least six months after discharge. The abnormal findings on EEG and MRI significantly improved before discharge. In view of this clinical course, benzodiazepine therapy was thought to have successfully treated his illness.

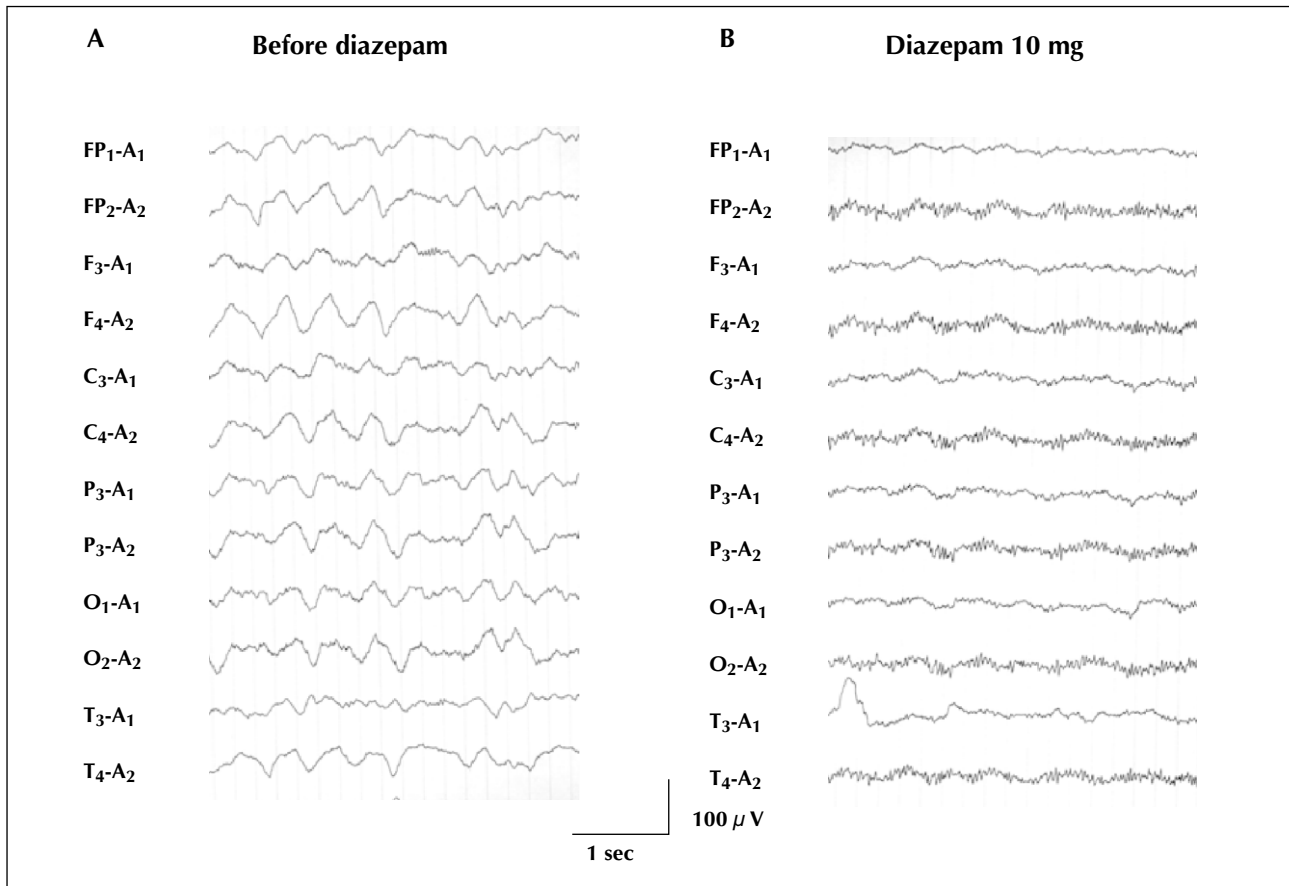


Figure 3. EEG before (A) and immediately after (B) intravenous injection of 10 mg of diazepam.

In (A) high amplitude, 1-3-Hz rhythmic activities were continuously seen, diffusely but more anteriorly on the right. The patient was mute, staring at one point.

In (B) the high amplitude slow activities were markedly diminished, while low-voltage, relatively rhythmic, 1-Hz activity remained bilaterally. The patient started to talk although it was jargon. He raised his hand following our instruction, but he could neither identify his own name nor name objects. This condition lasted for 20 minutes. The fast activities in the right hemisphere were judged to be an artifact of the EMG.

Herpes simplex virus was not detected by either PCR or chemiluminescence methods, which suggests the diagnosis to be different from herpes simplex encephalitis. The presence of other viruses was checked, but all were negative.

Functional neuroimaging

A positron emission tomography (PET) study with [^{11}C]-flumazenil was performed using a GE ADVANCE scanner (GE Medical Systems, WI, USA) on the 20th hospital day, one day before starting lorazepam treatment. We acquired the distribution volume image of summed activity during the period 20-40 minutes after injection of 370 MBq of flumazenil, which should enable semi-quantitative imaging of benzodiazepine receptor distribution (Mishina *et al.* 2000). Diazepam was not adminis-

tered before or during the scan. Tracer accumulation was significantly diminished in the right fronto-temporal area (*figure 2B*).

Cerebral blood flow (CBF) study with single photon emission computed tomography (SPECT) was performed twice during the acute stage of illness (on the 14th and 21st days in hospital). SPECT examination was performed using a three-headed gamma camera (Prism 3000, Picker, OH, USA) with 740 MBq of Tc-99m HMPAO as a radiotracer for each study. Attenuation correction was performed using ellipses outer line approximation and Chang's method (Chang 1978) (coefficient of 0.06/cm) adjusted for each slice. The same ellipse size was kept for different scans of the patient.

Scatter correction was not applied. The first baseline SPECT study revealed hyperperfusion in the right fronto-temporal region, where the flumazenil uptake which was tested 6 days after the first SPECT study, was reduced

(figure 4A). In the second SPECT study, a tracer was injected after the patient's consciousness improved following administration of 10 mg of diazepam. The hyperperfusion in the right fronto-temporal area turned out to be normal (figure 4B).

A fluoro-deoxyglucose (FDG) PET study was performed using a GE ADVANCE scanner (GE Medical Systems, WI, USA) with injection of 350 MBq of FDG on the 27th hospital day, at which time the patient was still in the acute phase of the illness, demonstrating no distinct decrease in glucose metabolism in that area (figure 2C).

Discussion

Because acute encephalitis is often accompanied by non-convulsive or convulsive epileptic attacks, it is very important to discuss first whether the patient has experienced such attacks.

Initially the patient showed automatisms and catalepsy, which support the diagnosis of catatonia. Usually, catatonic stupor is associated with minor EEG changes or low amplitude background activity. However, we reported relatively high amplitude slow activity in a patient with catatonic stupor with a diagnosis of dopa-responsive dystonia (Ihara *et al.* 2002). It has been reported that some cases of catatonic stupor are accompanied by relatively high amplitude slow activity (Suzuki *et al.* 2006). The EEG findings in the present patient are consistent with these findings, and should not necessarily be interpreted as epileptic activity.

It has been proposed that catatonic stupor itself might predispose patients to the development of epileptic seizures (Suzuki *et al.* 2006). Therefore, it may be noteworthy that the present patient manifested catatonic stupor, later followed by episodes of EPC.

With regard to the pathophysiology of catatonia in this case, because cortical glucose metabolism was not found to be decreased in the FDG-PET study while benzodiazepine receptor binding was found to be diminished in the FMZ-PET study, the catatonia is considered to be related to a postsynaptic rather than presynaptic abnormality at the cortical level, although there is a lack of longitudinal data and there exists a timing difference between imaging studies.

Furthermore, the increase in CBF in the same region is unlikely to be related to the inflammatory process, because the abnormal hyperperfusion revealed by SPECT was improved by diazepam injection (figure 4B). Instead, it is more likely to be related to increased neuronal excitation or loss of inhibition. The high voltage, rhythmic slow activity on the EEG, which rapidly changed to low voltage slow activity after diazepam injection, supports this interpretation.

Flumazenil (FMZ) is a specific, high affinity neutral antagonist of the benzodiazepine-binding site of GABA_A receptors (Olsen *et al.*, 1990). 11C-FMZ PET provides a useful *in vivo* marker of GABA_A receptor binding (Maziere *et al.* 1984).

Considered together with the reduced benzodiazepine binding on FMZ-PET and the dramatic effect of benzodiazepine administration, the catatonic stupor in this patient might be postulated to be related to dysfunction of the inhibitory GABA system, rather than permanent neuronal loss in the frontotemporal area.

In humans, the distribution of benzodiazepine receptors has been mainly studied using PET and 11C-flumazenil or SPECT and 123-iodoflumazenil (Pappata *et al.* 1988, Persson *et al.* 1985).

Our patient also demonstrated low accumulation of flumazenil in the right frontotemporal area. However, since glucose metabolism was not decreased in the same area,

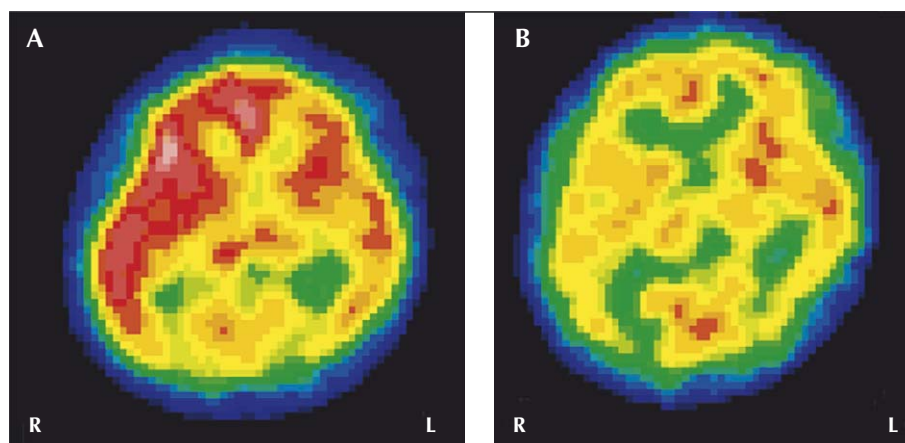


Figure 4. CBF measurement with HMPAO-SPECT before (A) and after (B) injection of 10 mg of diazepam. These images were acquired on the 14th (A) and 21st (B) hospital days, respectively. These are qualitative images. A) Note the increased CBF in the right frontal and temporal lobes. B) CBF decreased in the right hemisphere after injection of 10 mg of diazepam.

and as the catatonic stupor was pharmacologically reversible, it is unlikely that the reduction of flumazenil binding was due to neuronal loss. There has been no previous report of a flumazenil-PET study of catatonic patients. However, a SPECT study using ^{123}I -iomazenil revealed decreased tracer binding in the left superior frontal cortex in catatonic patients (Northoff *et al.* 1999). Using FDG-PET, Lauer *et al.* (2001) indicated that hypometabolism of the frontal cortex, especially on the left side, is part of the mechanism underlying catatonia. Moreover, Kaestner *et al.* (2008) described hypometabolism of the frontal cortex and the left temporal lobe in patients with catatonia induced by paraneoplastic encephalitis by means of FDG-PET. Considering these cases, not only the decrease in metabolism, but also the decrease in tracer binding showed laterality with left side predominance, while in our case, the patient showed decreased tracer binding on the right side. This might be related to the fact that our patient was left-handed, and this laterality should be further investigated in the future.

A patient with catatonic stupor owing to herpes encephalitis, who was described in the literature (Raskin and Frank 1974), showed focal slow activity on EEG in the right frontotemporal region; another case of catatonia resembling non-convulsive status epilepticus showed diffuse arrhythmic theta slowing without any epileptiform activity (Louis and Pflaster 1995). In the present case, the initial EEG recording showed focal intermittent irregular slow waves in the right frontotemporal area corresponding to the high intensity area on MRI. The patient later developed catatonic episodes, and the EEG showed continuous rhythmic, high amplitude slow activity diffusely more anteriorly on the right; this disappeared promptly after diazepam injection. Ihara *et al.* reported a patient with dopa-responsive dystonia manifesting a malignant syndrome with prolonged catatonia, whose EEG activities were markedly diminished after the diazepam injection (Ihara *et al.* 2002). The quick disappearance of continuous EEG slowing immediately after diazepam infusion supports the diagnosis of catatonia.

In summary, we suggest that abnormality of the frontotemporal cortex owing to an impaired inhibitory GABAergic system might be one of the pathophysiologic mechanisms causing catatonic stupor, and that it is clinically important to differentiate this mechanism from the mechanism underlying ictal events. □

Disclosures.

We disclose that this case report is a by-product of clinical observation and treatment of our patient although we planned and conducted the examinations performed during the clinical course. The general status of the patient was so severe, because of severe consciousness disturbance, high fever and apnea, that we were only able to perform

examinations when the patient was in remission; thus, there was a limitation to the number of examinations that could be performed. We express our gratitude to all of the medical staff associated with the clinical course of this patient.

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