Asterixis and Astatic Seizures in Association with Bilateral Insular Lesions in a Patient with Viral Encephalitis

Shinjiro Muneta, Yoriaki Yamashita*, Hiroshi Fukuda, Seiichiro Watanabe, Yoichi Imamura and Isao Matsumoto

We report a 48-year-old man who suffered from viral encephalitis and developed involuntary movements of the hands and astatic seizures as sequelae. T2-weighted magnetic resonance imaging (MRI) of the brain showed high intensity areas in the bilateral insulae. Electroencephalography (EEG) revealed spike and slow wave complexes and high-amplitude slow waves. The involuntary movements of the hands were diagnosed as asterixis by electromyography. Asterixis affected both hands. Administration of sodium valproate exacerbated asterixis and EEG findings, but treatment with clonazepam markedly improved these findings and astatic seizures. The present case indicates that insular lesions might also be responsible for the development of asterixis.

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Key words: negative myoclonus, clonazepam, electroencephalography, electromyography

Introduction

Asterixis is commonly observed in metabolic, anoxic or toxic encephalopathy associated with conditions such as severe liver disease, respiratory failure, heart failure and drug intoxication (1, 2). Asterixis observed in hepatic encephalopathy is known as flapping tremor or liver flap (3). Asterixis is also caused by focal brain lesions (1). However, there is no case report of asterixis resulting from viral encephalitis or from lesions of the insula. In this report, we describe the case of a patient who suffered from viral encephalitis and developed asterixis and astatic seizures as sequelae, in whom bilateral insular lesions were found by magnetic resonance imaging.

Case Report

A 48-year-old man had fever, headache and shaking chills on February 5, 1991. Since the symptoms did not improve and generalized convulsion attacks subsequently occurred, he was admitted to a hospital on February 9. His clinical course after admission is shown in Fig. 1. On admission, fever, generalized convulsions, myoclonus-like involuntary movements and disturbed consciousness were observed. His clinical course and laboratory findings indicated that he had viral encephalitis. His symptoms were not improved by acyclovir administration, but almost disappeared about 3 weeks after administration of adenine arabinoside (Ara-A). Subsequently, involuntary movements of the hands and upper and lower limbs, which were not improved by carbamazepine administration, were noted. Late in March 1991, fever and generalized erythema developed, and he suddenly fell down on the floor while talking on the phone in a standing posture. This episode of astatic seizure was accompanied by a transient loss of consciousness which lasted several minutes. He was admitted to our hospital for further evaluation and treatment on April 5, 1991.

Figure 1 shows serum titers of anti-herpes simplex virus (HSV) antibodies (CF and NT) and the results of cerebrospinal fluid (CSF) examination at different times between February 9 and 22. On the initial examination, anti-HSV antibodies were already positive and showed no significant changes during this period. As for anti-HSV antibodies in CSF (enzyme-linked immunosorbent assay: ELISA), the IgG antibody showed a positive ratio of 1 : 350–400, but the IgM antibody remained negative during this period. CSF examination showed an increased number of lymphocytes in the acute stage, but the glucose and protein concentration were normal. Serum antibodies against varicella-zoster virus and Japanese encephalitis virus were negative. T2-weighted (2,000/100/2, TR/TE/excitations) magnetic resonance imaging of the brain showed high intensity areas in the bilateral insulae extending to part of the right frontal lobe (Fig. 2).

On admission to our hospital, he was conscious. His blood pressure was 110/60 mmHg, pulse rate was 92 per minute and regular, and body temperature was 37.1°C. There were no
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<table>
<thead>
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<th>Date</th>
<th>1991.2.10</th>
<th>3.10</th>
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<tbody>
<tr>
<td>Therapy</td>
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<tr>
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</tr>
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<td>Ara-A</td>
<td>250 (mg/day)</td>
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<tr>
<td>carbamazepine</td>
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<tr>
<td>BT (°C)</td>
<td>37</td>
<td>&gt;w</td>
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<tr>
<td></td>
<td>35-</td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td></td>
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<tr>
<td>Myoclonic jerk</td>
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<tr>
<td>Asterixis</td>
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**Figure 1. Clinical course after the patient’s admission to the first hospital.** Fever, myoclonic jerks, generalized convulsions and disturbed consciousness were observed on admission. These symptoms were improved by administration of adenine arabinoside. Cerebrospinal fluid examination showed an increased number of lymphocytes in the acute stage. Ara-A: adenine arabinoside, BT: body temperature, HSV: herpes simplex virus, CF: complement fixation test, NT: neutralization test, CSF: cerebrospinal fluid, N: neutrophil, L: lymphocyte.

<table>
<thead>
<tr>
<th>Serum HSV Ab (CF)</th>
<th>2/9</th>
<th>2/12</th>
<th>2/15</th>
<th>2/22</th>
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<tr>
<td>(NT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF cell (/mm³)</td>
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<td>22</td>
<td>12</td>
<td>1</td>
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<tr>
<td>(N:L)</td>
<td>(6:17)</td>
<td>(2:20)</td>
<td>(1:11)</td>
<td>(1:0)</td>
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<tr>
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<td>40</td>
<td>32</td>
<td>25</td>
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<td>sugar (mg/dl)</td>
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<td>81</td>
<td>66</td>
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Horizontal elevation of the bilateral hands and arms induced intermittent downward movements of the hands at the wrist and intermittent drops of the upper limbs at the shoulder, suggesting flapping tremor. Neurological examination showed no other abnormal findings. Generalized erythema was present. Laboratory examination showed mild inflammatory findings (erythrocyte sedimentation rate 17 mm/h, CRP 0.67 mg/dl) and abnormal liver function tests (aspartate aminotransferase 123 IU/l, alanine aminotransferase 316 IU/l, lactate dehydrogenase 652 IU/l, alkaline phosphatase 721 IU/l, glutamyltranspeptidase 326 IU/l). The blood ammonia concentration was normal. The HBs antigen, anti-HA antibody (IgM) and anti-HCV antibody were negative. The serum anti-HSV antibody titer (CF) was 1 : 16. The electroencephalogram (EEG) before drug treatment revealed spike and slow wave complexes and high-amplitude slow waves in all leads without laterality (Fig. 3A). On surface electromyograms of the forearm, electrical silent periods (50-150 msec) occurred simultaneously in the wrist extensor and flexor muscles of the left forearm. The silent periods were followed by the drop phenomenon of the left hand indicated by a downward movement in the accelerometer trace (Fig. 4).

These findings suggested that the tremor of his hands was asterixis. Although the electrical silent periods occurred in both forearms, their appearance was not synchronized on the right and left sides. The association between EEG and electrical silent periods was unclear. The cortical long loop reflex (C-reflex) was negative.
Figure 2. T2-weighted (2,000/100/2, TR/TE/excitations) magnetic resonance imaging of the brain showing high intensity areas in the bilateral insulae which extended to part of the right frontal lobe. A) Horizontal section: The scan level of the right panel is 1.0 cm cranial to that of the left panel, B) Coronal section: The scan level of the right panel is 1.0 cm ventral to that of the left panel.

Figure 5 shows the clinical course of the patient after his admission to our hospital. The fever, generalized erythema and abnormal liver function rapidly subsided after carbamazepine was discontinued, suggesting that these findings were due to allergy to carbamazepine. Asterixis was not improved by administration of sodium valproate (600 mg/day), and on the contrary it was rather aggravated by an increased dose of the drug (1,200 mg/day). After all anticonvulsant drugs were discontinued, astatic seizure recurred while the patient was standing in front of a washstand. Asterixis was not improved by phenytoin, either, but was markedly improved by clonazepam. The EEG also showed aggravation of the frequency of spikes and high-amplitude slow waves after administration of sodium valproate but there was marked improvement of these findings after clonazepam administration (Fig. 3B). During the patient’s clinical course, no disturbance of consciousness was observed, and the blood ammonia concentration was normal. After being discharged, the patient has suffered only one episode of astatic seizure which occurred while he was playing pinball, but asterixis almost disappeared. The patient is still under treatment with clonazepam (3.0 mg/dl). The titer of anti-HSV antibodies in CSF (ELISA) measured at the outpatient clinic 3 months after discharge was 1:20 for IgG and negative for IgM.

Discussion

Asterixis, also called negative myoclonus, is caused by intermittent interruption of muscle contraction needed to maintain an anti-gravitational posture (1). In general, asterixis is observed in metabolic or anoxic encephalopathy. In the present patient, no disturbance in consciousness was observed, the blood ammonia concentration was normal during his clinical course and laboratory findings did not reveal any metabolic disorder. His clinical course and CSF findings indicated viral encephalitis, probably due to HSV. However, brain lesions localized in the bilateral insulae without involving the temporal lobe are not typical of herpes simplex encephalitis or any other viral encephalitis. It is interesting that the insulae were specifi-
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Figure 3. Electroencephalogram before drug treatment (A: April 25, 1991). Spike and slow wave complexes and high-amplitude slow waves were observed. These findings markedly improved after administration of clonazepam (B: May 13, 1991).

cally affected by viral encephalitis in the present patient.

Viral encephalitis is often associated with myoclonus as a complication, but, to our knowledge, there have been no reports of viral encephalitis showing negative myoclonus (asterixis) alone. The present patient developed myoclonic seizures in the acute stage. Myoclonus is classified into two types: positive myoclonus due to involuntary muscle discharges and negative myoclonus due to interruption of muscle discharges. These two types are often observed together (4). In the present patient, positive myoclonus may have disappeared after the acute stage, and thus only negative myoclonus remained. Astatic seizures were also observed in the present patient. These may have resulted from the sudden disappearance of strength of muscle groups (asterixis) in the trunk and lower limbs that are necessary to maintain the standing posture.

Asterixis also occurs in patients with localized brain lesions such as cerebral hemorrhage, cerebral infarction, and brain tumors, and asterixis due to localized brain lesions is usually unilateral (1, 5). The reported localized areas include the thalamus, putamen, parietal region, internal capsule, medial area of the frontal lobe, midbrain, pons and medulla oblongata (6-11). However, there are no reports of asterixis in patients with lesions localized in the insula as shown in the present case.

The mechanism of asterixis is still unclear. On the EEG of patients with asterixis, spikes sometimes occur in accordance with start of the interruption of muscle discharges. In the present patient, there was no association between the interruption of muscle discharges and EEG. Ugawa et al (12, 13) and Yokota and Tsukagoshi (14) electrophysiologically evaluated asterixis using the silent period-locked averaging method, and observed negative sharp waves in the contralateral central area. They suggested that asterixis is due in part to abnormal activity in the motor field in the cerebral cortex.

Asterixis can also be seen as a side effect of various anticonvulsant drugs such as carbamazepine and phenytoin (anti-convulsant asterixis) (1, 15). Sodium valproate sometimes induces hyperammonemia due to liver injury. In the present patient, asterixis did not improve after the discontinuation of carbamazepine and an increased dose of sodium valproate did not induce hyperammonemia, suggesting that the asterixis observed in the present patient was not caused by anticonvulsant drugs. Since asterixis also arises from intoxication of various drugs other than anticonvulsant drugs (16, 17), drugs administered in such patients should be carefully examined. Benzodiazepine anticonvulsant drugs such as nitrazepam and clonazepam are known to be effective against myoclonus. In the
Figure 4. Surface electromyogram of wrist extensor and flexor muscles of the forearm. The electrical silence periods (50–150 msec) (thick line) tended to occur simultaneously in the muscles of the left forearm. The drop phenomenon observed in the left hand (closed circle), as shown by the accelerometer trace, was seen shortly after each silent period. EEG: electroencephalogram, Acc: accelerometer, Ext: extensor, Flex: flexor.

present patient, clonazepam markedly improved asterixis and prevented astatic seizures.

The present case indicates that insular lesions might also be responsible for the development of asterixis and astatic seizures. Although focal lesions at various sites in the brain have reported as responsible for asterixis, the mechanism of asterixis has not yet been systematically explained. Further studies on the neural circuit in the brain for the maintenance of muscle tension are needed to clarify the pathogenesis of asterixis.

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References

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![Graph showing dates and medications](image)

**Figure 5.** Clinical course of the patient after admission to our hospital. The fever and generalized erythema disappeared after discontinuation of carbamazepine administration. Asterixis was not improved by sodium valproate or phenytoin, and on the contrary it was aggravated by an increased dose of sodium valproate. Asterixis and astatic seizures almost completely disappeared after treatment with clonazepam was started.