Case Report

A case of autoimmune encephalitis with involuntary movements as the first symptom and suspected association with mumps virus infection

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Abstract: This case involved a 72-year-old woman. From the day after mitral annuloplasty, a fever over 37°C and ballismus-like involuntary movements of the right upper and lower limbs appeared. A few month later, involuntary movements spread throughout the body, and she developed impairment of consciousness and difficulty speaking and eating. Levels of protein in cerebrospinal fluid were high. Positive results were seen for serum mumps immunoglobulin G and M antibody. Because steroid pulse therapy proved effective, we suspected autoimmune encephalitis associated with mumps virus infection.

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Key words: involuntary movement, mumps virus, autoimmune encephalitis, steroid pulse therapy

Introduction

A variety of autoimmune encephalitides are negative for specific antibodies and triggered by infection, drugs, or vaccines. Mumps virus has a high affinity for the central nervous system, but complications of encephalitis after mumps virus infection are extremely rare, at around 0.1%[1)2)]. Many issues regarding the clinical picture and effective treatment methods remain unclear. We encountered a case of autoimmune encephalitis with involuntary movements as the first symptom and suspected an association with mumps virus infection. This case is therefore reported with reference to the literature.

Case

Patient: A 72-year-old woman

Past medical history: mitral insufficiency, hypertension, hyperlipidemia, hyperthyroidism, mumps (twice in childhood)

Family history: hypertension in her father, Alzheimer's disease in her mother.

History of present illness: One day in July of 72-year-old, mitral annuloplasty was performed at another hospital for mitral insufficiency. From the day after the surgery, a fever over 37°C and ballismus-like involuntary movements of the right upper and lower limbs appeared. Involuntary movements continued even after the fever went down. She visited our hospital for neurosurgery and symptoms were suspected to be associated with intraoperative cerebral ischemia. Involuntary movements were temporarily reduced after administration of haloperidol. However, two weeks later drug eruptions appeared, and oral medication was therefore changed to sulpiride. Involuntary movements subsequently spread to the entire body over time about three months, and maintaining a sitting position and eating food became difficult. In addition, she was admitted to our department in November of the same year after she began to repeat verbose and unrelated words.

Findings on admission: Vital signs showed a temperature of 36.8°C, blood pressure of 92/63 mmHg, and heart rate of 92 beats/min. No swelling of the parotid glands was evident. A general internal medicine examination revealed no abnormalities. Glasgow Coma Scale score was E4V4M6, and Hasegawa dementia rating scale-revised score was 27/30. She was able to answer questions, but inclusion of verbose and unrelated words in responses was conspicuous. No abnormalities were identified in the cranial nerves, limb muscle strength, or limb sensation. No differences were evident between left and right tendon

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reflex of the extremities, and pathological reflexes were also negative. No abnormal breathing or autonomic neuropathy were observed. She repeated blink strongly of both eyes frequently, and she swiftly turned her head from side to side. Movements of throwing her limbs violently to the right side and flexing movements were quickly repeated, and the tips of the right toes were repeatedly rotated into an equinus position. She found it difficult to suppress these movements on her own initiative. Rigidity of the limbs and resting tremor were not observed, and no meningeal irritation was evident. Walking was difficult, but maintaining a sitting position was possible.

Laboratory findings: No abnormalities were seen in blood count or coagulation ability. Biochemical tests showed no increase in inflammatory response and no abnormalities in electrolytes or blood glucose levels. Thyroid stimulating hormone 0.49 μIU/m*l*; free T3 1.55 pg/m*l*; free T4 1.08 ng/d*l*. Levels of NH_3, lactic acid, pyruvic acid, vitamin B1, vitamin B12, folic acid, magnesium, ceruloplasmin, angiotensin 1 converting enzyme, and intact parathyroid hormone were all within normal range. In tumor-related areas, all antibodies against CEA, AFP, CA125, CA19-9, IL-2R concentration, AMPH, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr (DNER) were negative. Immunologically, results for anti-nuclear antibody, anti-ds-DNA-IgG antibody, rheumatoid factor, ANCA, IgG4, anti-GAD antibody, anti-TPO antibody, anti-thyroglobulin antibody, anti-ganglioside antibody, anti-NMDAR antibody (cerebrospinal fluid [CSF]), anti-LGI1 antibody (CSF), and anti-CASPR2 antibody (CSF) were all negative. Regarding infectious diseases, results for β-D glucan, cryptococcus, T-SPOT, and HIV were negative. Prior infections with herpes simplex virus, varicella-zoster virus, EB virus, and cytomegalovirus were all confirmed. Mumps virus antibody was measured twice by enzyme immunoassay, and both were IgG antibody-positive and IgM antibody-positive (day 8; IgG 6.6/IgM 1.96, day 23; IgG 4.8/IgM 1.51). Macroscopic examination showed CSF was pale red and turbid, with an initial pressure of 60 mmH_2O. Results for CSF were: cell count, 1/μ*l*; protein, 124 mg/d*l*; sugar, 71 mg/d*l*; IL-6, 17.7 pg/m*l*; myelin basic protein, <31.3 pg/m*l*. Oligoclonal band was negative. Bacterial culture, acid-fast bacillus culture, and ink staining of CSF were all negative, and no atypical cells were detected on CSF cytology.

Image findings: No abnormalities were found on thoracoabdominal simple CT and pelvic MRI. Cerebrovascular accidents, neoplastic lesions, and inflammatory findings were not found on contrast-enhanced MRI of the head. No abnormal waves include focal slowing/seizures, lateralized periodic discharges, and extreme delta brush were found in any of the electroencephalogram tests performed twice (day 3 and 16). Single photon emission computed tomography (SPECT) of the brain showed a strong increase in accumulation in the left thalamus, suggesting increased blood flow (Fig. 1A).

Clinical course (Fig. 2): Since movements of the face and limbs disappeared during sleep, involuntary movements were not considered contradictory. Involuntary movements were exacerbated even after hospitalization, and impaired consciousness also appeared on day 5 of illness. Strange voices were repeated, making conversation and food intake difficult. Based on the above findings, the case was considered similar to the previously reported[3] mumps-related encephalitis/encephalopathy, and an autoimmune mechanism was suspected. Steroid pulse therapy was started with methylprednisolone at 1 g/day for 3 days. Since the first time of steroid pulse therapy showed a marked reduction in involuntary movements, a total of three times of steroid pulse therapy were performed. Table 1 shows the results of CSF examination before treatment and after the second and third steroid pulse therapy. Oral steroid therapy (prednisolone, 0.5 mg/kg/day) was then started and tapered. A second brain SPECT on hospital day 17 showed that the accumulation in the left thalamus had disappeared (Fig. 1B). Level of consciousness improved over time, and conversation and food intake became possible. No sequelae other than muscle weakness associated with long-term bed rest, and the patient was transferred to another hospital on hospital day 71.

Consideration

Autoimmune encephalitis may display few abnormalities in blood tests or on imaging, and antibodies that can be measured in clinical practice are limited. Graus et al have proposed clinical diagnostic criteria for autoimmune encephalitis[4]. This case was a subacute course with new focal central nervous system findings, and many differential diseases were excluded. Therefore, it was judged to correspond to possible autoimmune encephalitis. On the other hand, no abnormal findings were found in CSF examination, electroencephalogram examination, and head MRI examination as mentioned by Abboud et al[5]. In this case, parotid swelling was not seen but a fever was seen before the onset of involuntary movements. The patient had a history of twice mumps infections in early childhood, and both measurements of mumps virus antibodies by enzyme immunoassay were IgG and IgM antibody-positive, and symptoms improved after steroid pulse therapy. Based on the above, reinfection with mumps virus was considered associated with the development of autoimmune encephalitis. Previously, IgM antibody measurement by enzyme immunoassay has shown problems such as long-lasting tailing after infection and detection in healthy adults. However, improvements in antibody detection reagents have reduced nonspecific positivity and have resulted in a better correlation between IgM antibody results and clinical course[6]. Based on the report by Ihara et al., mumps

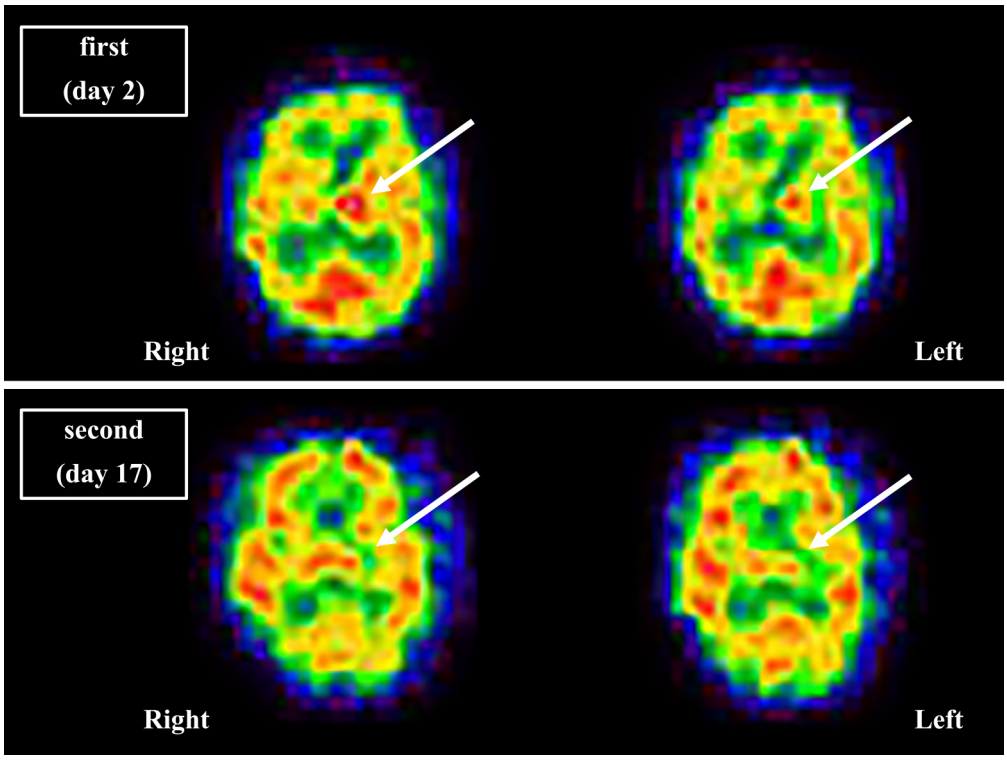

Fig. 1　Brain SPECT.
The increased accumulation observed in the left thalamus has disappeared after steroid pulse therapy (arrow).

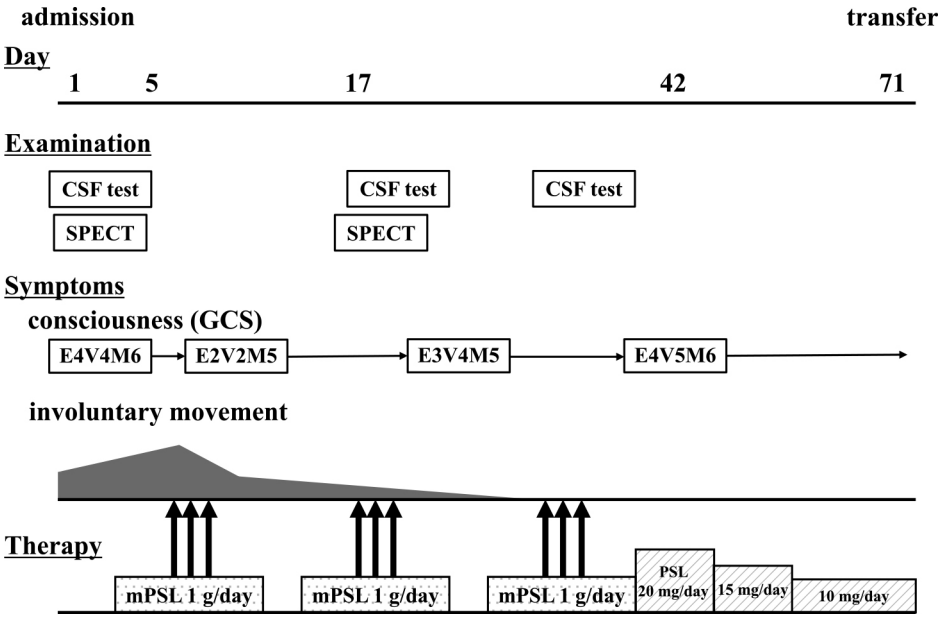

Fig. 2　Clinical course.
A total of three administrations of steroid pulse therapy reduced involuntary movements and improved consciousness. The patient was transferred to another hospital without any obvious sequelae. CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; mPSL, methylprednisolone; PSL, prednisolone; SPECT, single photon emission computed tomography.

Table 1 Cerebrospinal fluid findings: Steroid treatment improved macroscopic findings and protein quantification.

	day 2	day 18	day 32
macroscopic findings	pale red/ turbidity	pale yellow/ transparent	colorless/ transparent
number of cells (/μl)	1	1	<1
polynuclear cells (/μl)	1	<1	<1
mononuclear cells (/μl)	<1	1	<1
protein (mg/dl)	124	102	36
glucose (mg/dl)	71	106	119

reinfection is most suspected when there is a history of mumps, IgM antibody is positive, and IgG antibody is also positive[7]. Ochiai et al. proposed that the mumps virus serum IgM antibody titer <2.5 and serum IgG antibody titer >25.8 as a diagnostic criterion for mumps reinfection[8]. However, since this diagnostic criterion was intended for children, it is controversial whether it can be applied to adults as it is. It has been reported that the avidity measurement of IgG antibody is useful for distinguishing between primary infection and reinfection[9], but this case has not been measured. In this case, both IgG and IgM antibody were lower in the second time than in the first time. Since this was measured about 5 months after the fever suggesting infection, it is possible that both of them were looking at the values during the recovery period.

Mumps virus is a highly infectious RNA virus belonging to the Paramyxoviridae family, spread by droplet infection and contact infection. Basically, persistent infection does not result[10], but the virus shows high affinity for the central nervous system, and 1–10% of patients reportedly develop meningitis due to mumps virus, and 0.1% develop encephalitis[1)2)]. As mechanisms of encephalitis after mumps infection, both primary encephalitis due to direct invasion of the virus and secondary encephalitis involving an immune mechanism have been considered[1)3)]. Various clinical features have been described in descriptions of encephalitis after mumps infection in adults, such as apallic syndrome after the onset of convulsions[3], brainstem encephalitis[11], limbic encephalitis[12], myelitis[13], and subarachnoid hemorrhage[14]. However, this appears to be the first case in Japan to show involuntary movements as the first symptom.

Involuntary movements are movements unrelated to intent and are defined as purposeless movements that are difficult to suppress by the will[15]. Generally, such movements may be persistently observed while awake and disappear during sleep. The basal ganglia, which consists of the caudate nucleus, putamen, external globus pallidum and internal segment, subthalamic nucleus, substantia nigra pars compacta, and pars reticulata, is involved in programming movements. Disorders of the basal ganglia are thus thought to lead to involuntary movement[16)17)]. In addition to drug-induced causes, such disorders can be triggered by cerebrovascular accidents, neurodegenerative diseases, malignant tumors, and infectious diseases. In this case, cerebrovascular accidents, neurodegenerative diseases, malignant tumors were negative. When the mitral annuloplasty, although she was administered general anesthetics, she was not administered transfusions. And after the operation, electrolytes and osmotic pressure of serum were no abnormality. Immunotherapy reduced involuntary movements and eliminated the accumulation seen in the left thalamus on brain SPECT, suggesting that immune-mediated inflammation may have occurred at that site.

The limitations of this report were that PCR measurement of mumps virus in serum and CSF could not be performed, the avidity of IgG antibody could not measure, and the relevance of surgery could not be denied. Encephalitis should also be differentiated when involuntary movements are diagnosed. If an immune-mediated mechanism is assumed to be the cause, immunotherapy from an early stage should be considered.

※The authors declare there is no conflict of interest relevant this article.

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