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Highlights:

- Autoimmune epilepsy can be seen in the course of anti-MOG associated disease
- Cortical abnormality can be undetectable on routine MRI
- Early suspicion is necessary even in patients with persistent symptoms such as aphasia

Aphasic status epilepticus preceding tumefactive left hemisphere lesion in anti-MOG antibody associated disease

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Key words: Myelin oligodendrocyte glycoprotein; Autoimmune epilepsy; Cortical encephalitis; Aphasia; Tumefactive demyelinating lesion

Abstract:

Introduction: Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have recently been associated with epilepsy with FLAIR hyperintense cortical lesions on MRI. Association between anti-MOG antibodies and epilepsy without detectable structural brain lesion on MRI is unknown.

Case report: A 48-year-old right-handed man with a four-and-a-half year history of anti-MOG antibody associated demyelinating disease presented with persistent global aphasia. Brain MRI showed no new lesion or cortical lesion in the left hemisphere. Electroencephalogram, magnetoencephalography, and brain perfusion single-photon emission computed tomography suggested epileptic foci in the left temporal and parietal lobes, and the patient's aphasia transiently responded to intravenous diazepam, compatible with aphasic status epilepticus. Cerebrospinal fluid showed mildly elevated cell count and positive oligoclonal bands. The patient only partially responded to antiepileptic drugs but responded to steroid pulse therapy. Six months later, the patient again exhibited global aphasia. Brain MRI showed tumefactive white matter lesion in the left temporo-parietal lobes.

Conclusion: Autoimmune epilepsy without obvious causative lesion on MRI can be seen in the course of anti-MOG antibody associated demyelinating disease. The subsequent emergence of tumefactive lesion closely located to the epileptic foci may suggest some association between autoimmune epilepsy and demyelinating lesions.

Introduction:

Antibodies against myelin oligodendrocyte glycoprotein (MOG) have been related to acute disseminated encephalomyelitis, recurrent optic neuritis, and neuromyelitis optica (Ramanathan et al., 2016). Recent studies have shown that they are also related with tumefactive demyelinating lesions (Zhou et al., 2017), and epilepsy associated with cortical

lesions (Hamid et al., 2018; Ogawa et al., 2017).

Aphasic status epilepticus is a rare form of nonconvulsive status epilepticus due to localized dysfunction of language process in the dominant hemisphere. It is usually caused by structural lesion detected on magnetic resonance imaging (MRI) in the dominant hemisphere.

We herein report a right-handed man with anti-MOG antibody positivity presenting with aphasic status epilepticus without detectable structural left hemisphere abnormality, 6 months before the emergence of tumefactive white matter lesion in the left hemisphere.

Case report:

A 43-year-old right-handed man presented with a 2-week history of headache and dizziness after upper respiratory infection followed by spastic paraplegia without sensory disturbance. Brain MRI showed tumefactive white matter lesion in bilateral frontal lobes and corpus callosum involving the cortex (Fig. 1A,B). Spinal cord MRI showed no abnormality. Cerebrospinal fluid (CSF) showed elevated cell count (45/ μ L) and myelin basic protein (MBP) (> 700 pg/mL), and positive oligoclonal bands (6 bands). Brain biopsy showed demyelination predominantly affecting the perivascular white matter, and the patient responded to steroid pulse therapy. Disinhibition and attention disturbance remained. The patient experienced two relapses in the subsequent 4 years, with emergence of white matter lesion in right temporal and parietal lobes (Fig. 1C,D). Serum anti-MOG-IgG antibodies measured by cell-based assay turned out to be positive (titer of 1:2048 during first attack, 1:4096 during second attack, and 1:1024 during third attack). The patient had no remaining symptoms related to language. CSF showed normal cell count and negative oligoclonal bands at last follow-up after steroid pulse therapy.

Four-and-a-half years after initial presentation, at the age of 48, the patient presented with a 2 week history of headache and difficulty in speaking after upper respiratory infection followed by generalized tonic seizure. On admission, the patient was alert but could only

speaking simple words irrelevant to the context and could not obey simple commands, and thus was considered to suffer from global aphasia. Brain MRI showed no new lesion or cortical lesion in the left hemisphere (Fig. 1E,F). CSF showed mildly elevated cell count (11/ μ L) and positive oligoclonal bands (7 bands) with normal MBP (< 40 pg/mL). Electroencephalogram (EEG) showed continuous periodic high amplitude delta waves in the left temporal channels (Fig. 2), and intravenous diazepam transiently relieved the patient's aphasia. Magnetoencephalography (MEG) analysis showed expected location of ictal foci in the left temporal and parietal lobes (Fig. 1G,H). Brain perfusion single-photon emission computed tomography (SPECT) was also consistent with epileptic foci in the left temporal and parietal lobes (Fig. 1I,J). Aphasic status epilepticus was suspected and oral carbamazepine 600 mg, topiramate 400 mg, and clonazepam 2 mg per day were initiated. However, EEG still showed intermittent bursts of high amplitude delta waves in the left temporo-parietal channels, and the patient remained aphasic with only transient improvement after intravenous diazepam. Although no white matter or cortical lesions were observed in the left cerebral hemisphere where epileptic discharge resides, we decided to start steroid pulse therapy due to refractory aphasic status epilepticus and abnormal CSF findings. The patient improved after 3 courses of steroid pulse therapy and became able to speak fluently and understand complex commands. CSF showed normal cell count and negative oligoclonal bands after steroid therapy. EEG showed disappearance of high amplitude delta waves in the left temporo-parietal channels. Serum anti-MOG antibodies remained to be high during the attack with a titer of 1:2048. Antibodies against N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated proteinlike 2 (CASPR2), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and γ -aminobutyric acid-B receptor (GABA(B)R) in the CSF were tested by indirect immunofluorescence using commercially available kits (Euroimmun, Lübeck, Germany), and were all negative. The

patient was unable to take daily oral steroids.

Six months later, the patient started to have difficulty in repeating sentences. Brain MRI showed new white matter lesion in the left temporal lobe (Fig.1K,L). He eventually exhibited global aphasia, and the white matter lesion enlarged to involve left frontal and parietal lobes (Fig.1M–O). EEG showed no epileptic discharge. Serum anti-MOG antibodies remained to be high with a titer of 1:2048. The patient responded to four courses of steroid pulse therapy (Fig.1P) and is in remission after starting 10 mg of prednisolone per day for the subsequent 7 months. Optic neuritis has not been observed during the course.

Discussion:

Our patient suffered from aphasic status epilepticus without cortical abnormality detected on routine MRI during the course of anti-MOG antibody associated demyelinating disease. CSF findings and response to steroids were consistent with autoimmune epilepsy. After six months, tumefactive white matter lesion emerged closely located to the epileptic foci.

Since MOG is known as a component of myelin, it has been related with demyelinating white matter diseases. However, epilepsy associated with cortical encephalitis detected as FLAIR hyperintense cortical lesions has recently been reported in anti-MOG antibody positive patients (Ogawa et al., 2017). Different underlying pathophysiology for these two conditions are proposed (Ogawa et al., 2017). However, cortical encephalitis and demyelinating events such as optic neuritis and myelitis have been reported in same patients (Fujimori et al., 2017; Ogawa et al., 2017; Sugimoto et al. 2018). Our patient differed from these reports in that FLAIR hyperintense cortical lesion was not detected at the epileptic foci on MRI despite severe epilepsy. Recently, Ramanathan et al. have also reported isolated seizures without cortical abnormality detected on MRI in anti-MOG antibody positive children (Ramanathan et al., 2018). It is unclear whether MRI invisibility in these patients

was due to different pathology or merely a sensitivity issue in MRI. Nevertheless, these cases suggest that autoimmune epilepsy should be suspected regardless of MRI abnormality in anti-MOG antibody positive patients.

The subsequent emergence of tumefactive white matter lesion close the epileptic foci in our patient may suggest some association between these two events. Ramanathan et al. have recently reported a 3-year-old female with anti-MOG antibody positivity presenting with isolated focal seizures 8 months prior to subsequent demyelinating brain lesion (Ramanathan et al., 2018), although the authors did not report the relationship of anatomic location between these events. Our case raise the possibility that epilepsy preceding demyelinating lesions in anti-MOG positive patients may have some anatomical relationships with subsequent demyelinating events. Further studies are warranted to elucidate the relationship between epilepsy and demyelination in anti-MOG antibody positive patients.

Another important finding is that persistent aphasia was due to aphasic status epilepticus in the absence of structural lesion detected in the dominant hemisphere. Although EEG only showed lateralized slow wave, thorough evaluation including benzodiazepine trial, MEG, and brain perfusion SPECT was useful in the diagnosis. Epilepsy should be kept in mind even in patients presenting with persistent aphasia in the course of anti-MOG antibody associated disease.

In conclusion, autoimmune epilepsy without obvious MRI lesion causing aphasic status epilepticus can be seen in the course of anti-MOG antibody associated demyelinating disease. Further studies are needed to clarify the characteristics of epilepsy, cortical involvement, and their association with demyelinating events in anti-MOG antibody positive patients.

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Figure legends:

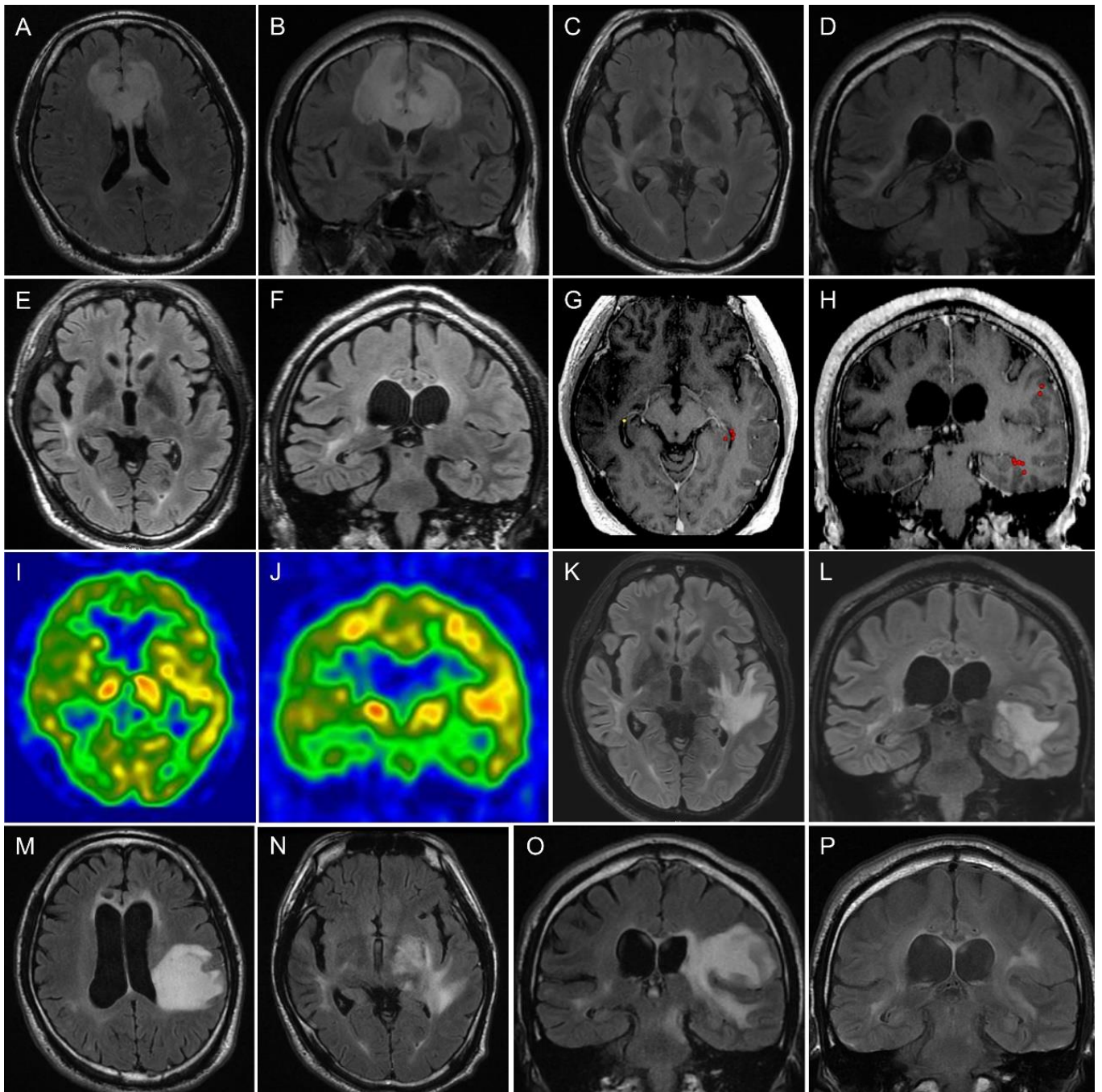


Figure 1. Radiological and magnetoencephalography studies. (A, B) Axial (A) and coronal (B) fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRI) performed at initial presentation. High intensity tumefactive white matter lesion is seen in bilateral frontal lobes and corpus callosum. (C, D) Axial (C) and coronal (D) FLAIR images

obtained 5 months before aphasic status epilepticus. High intensity white matter lesion is seen in right temporal lobe. (E, F) Axial (E) and coronal (F) FLAIR images obtained while the patient suffered from aphasic status epilepticus. No abnormality is seen in the left hemisphere. (G, H) Axial (G) and coronal (H) gadolinium enhanced T1-weighted MRI images while the patient suffered from aphasic status epilepticus. Red dots represent the expected ictal foci from magnetoencephalography analysis, which reside in left temporal and parietal lobes. No abnormal enhancement is noted. (I, J) Axial (I) and coronal (J) brain perfusion single-photon emission computed tomography studies while the patient suffered from aphasic status epilepticus. Increased cerebral blood flow suggesting epileptic foci is seen in left lateral temporal and parietal lobes. Mild increased blood flow is also seen in left pars opercularis. (K, L) Axial (K) and coronal (L) FLAIR images obtained while the patient suffered from mild impairment of word repetition 6 months after the first episode of aphasia. High intensity white matter lesion is seen in the left temporal lobe. (M–O) Axial (M,N) and coronal (O) FLAIR images obtained while the patient suffered from global aphasia 8 months after the first episode of aphasia. White matter lesion enlarged and became tumefactive, seen in left frontal, parietal, and temporal lobes. (P) Coronal FLAIR image after four courses of steroid pulse therapy. High intensity lesion mostly improved.

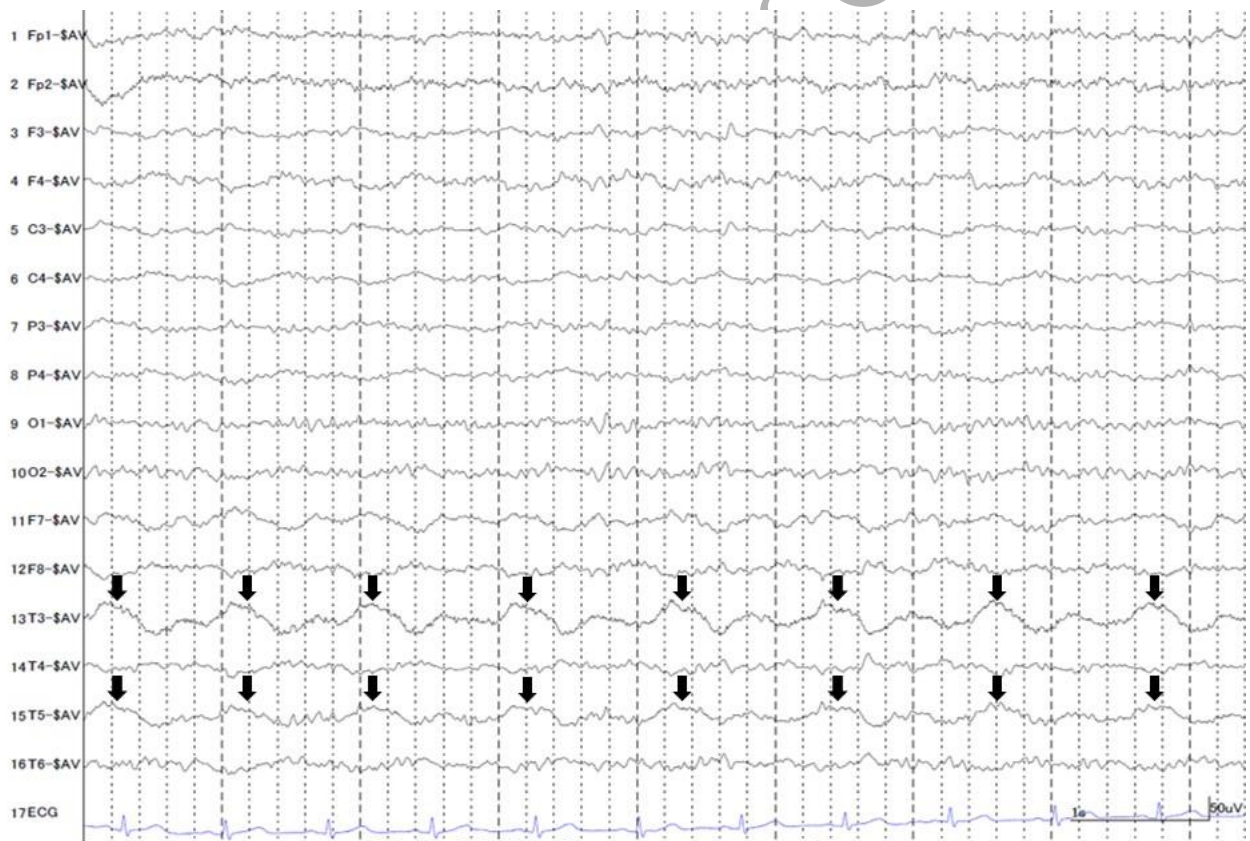


Figure 2. Electroencephalogram of the patient while the first episode of aphasia. Average reference recording. Continuous high amplitude delta waves are noted in the left temporal channels.