Limbic Encephalitis Associated with Anti-Voltage-Gated Potassium Channel Complex Antibodies as a Cause of Adult-Onset Mesial Temporal Lobe Epilepsy

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Abstract: Recently, some reports have indicated that limbic encephalitis associated with anti-voltage-gated potassium channel complex antibodies (VGKC-Ab) is a cause of adult-onset mesial temporal lobe epilepsy (MTLE). We report a 53-year-old woman who had her first epileptic seizure at the age of 50 years old. Examination by 3-Tesla brain MRI revealed left hippocampal high signal intensity and swelling on fluid-attenuated inversion recovery (FLAIR) and T2-weighted imaging at 2 months after her first seizure. The patient received intravenous methylprednisolone and carbamazepine 300 mg/day. One month later, MRI revealed improvement of her left hippocampal abnormalities. Thereafter, she had no seizures, however, three years after her first seizure, EEG revealed a seizure pattern in the left temporal region. Brain MRI revealed left hippocampal high signal intensity and brain fluorodeoxyglucose positron emission tomography revealed hypermetabolism. Her serum VGKC-Ab levels were 118 pM(normal < 100 pM). Intravenous methylprednisolone therapy was reinitiated. Two months later, her hippocampal abnormalities had improved and 3 months later her VGKC-Ab levels decreased to 4.4 pM. Remission of the epileptic seizures was also observed. This MTLE in the middle age was considered as limbic encephalitis associated with anti-VGKC-Ab. In cases of unexplained adult-onset MTLE, limbic encephalitis associated with anti-VGKC-Ab, which responds well to immunotherapy, should be considered in the differential diagnosis.

Keywords: limbic encephalitis, anti-VGKC antibodies, adult-onset, mesial temporal lobe epilepsy.

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Introduction

Mesial temporal lobe epilepsy (MTLE) usually begins in childhood or adolescence and is frequently associated with hippocampal sclerosis. Although little is known about the etiology of adult-onset MTLE [1], a few recent reports have indicated that limbic encephalitis associated with anti-voltage-gated potassium channel complex antibodies (VGKC-Ab) is a cause of adult-onset MTLE [1-5]. We report a case of VGKC-Ab-associated MTLE with recurrent limbic encephalitis that developed 3 years after onset. Recurrent limbic encephalitis associated with VGKC-Ab causing adult-onset MTLE has not been reported previously. In case...
of unexplained adult-onset MTLE, LE associated with VGKC-Ab should be considered in the differential diagnosis.

Case report

A 50-year-old woman with no significant past medical history had 3 complex partial seizures in a month characterized by a motionless stare; 1 seizure evolved to a secondarily generalized tonic-clonic seizure. She also felt a little forgetful but had no difficulties in her daily life. Examination by 3-Tesla brain MRI revealed left hippocampal high signal intensity and swelling on fluid-attenuated inversion recovery (FLAIR) and T2-weighted imaging (Fig.1A) at 2 months after her first seizure. Interictal electroencephalogram (EEG) revealed left temporal spikes. At two months after her first seizure, her serum VGKC-Ab levels were 61 pM (measured by radioimmunoassay using whole rabbit-brain homogenate, normal <100 pM) retrospectively. The patient received intravenous methylprednisolone (1 g/day × 3 days) and carbamazepine 300 mg/day. One month later, MRI revealed that her left hippocampal abnormalities had improved. She had no symptoms of complex partial seizures thereafter. Her left temporal spikes remained in the interictal EEG. In the next one year and 3 months, she had no seizures while on carbamazepine 300 mg daily. The carbamazepine was gradually reduced to 100 mg. Two years and ten months after presentation, an EEG revealed a seizure pattern in the left temporal region (Fig.2) with no clinical signs. The carbamazepine was increased back to 200 mg. Brain MRI repeated after 3 years revealed left hippocampal high signal intensity (Fig.1B). Brain fluorodeoxyglucose positron emission tomography revealed hypermetabolism (Fig.1C). Neuropsychological testing revealed a mild low score of delayed recall (85) in the Wechsler Adult Intelligence Scale Revised. Her serum VGKC-Ab levels were 118 pM. Her serum samples were negative for paraneoplastic antibodies (Ma, Ma1, amphiphysin, CV2, Ri, Yo, HuD). Hypothyroidism was noted, although the antithyroid antibodies were negative. Cerebrospinal fluid (CSF) examination revealed a mildly elevated protein level of 0.54 g/l, and intravenous methylprednisolone therapy was reinitiated (1 g/day × 3 days). Two months later, her hippocampal abnormalities had improved (Fig.1D), and 3 months later her VGKC-Ab levels decreased to 4.4 pM. In addition, remission of the epileptic seizures was also observed.

Written informed consent for measuring antibodies was obtained from the patient.

Fig. 1. Brain imaging. A. Brain MRI at disease onset. Axial fluid attenuated inversion recovery (FLAIR) image reveals left hippocampal high signal intensity and swelling. B. Brain MRI 3 years after disease onset. Axial FLAIR image reveals recurrent left hippocampal high signal intensity. C. Brain fluorodeoxyglucose-positron emission tomography (FDG-PET). Axial FDG-PET reveals hippocampal hypermetabolism (arrow). D. Brain MRI performed 2 months after the image in B. Axial FLAIR image reveals improvement of left hippocampal high signal intensity.
Discussion

It is easy to diagnose severe limbic encephalitis because of subacute onset of episodic memory impairment, disorientation and agitation, commonly associated seizures, hallucinations, sleep disturbance, and histological evidence of medial temporal lobe inflammation [6, 7]. However, it may be difficult to diagnose mild limbic encephalitis on the basis of clinical manifestations alone. Here we report a case with recurrent limbic encephalitis diagnosed during an MTLE follow-up, in which the patient demonstrated no clinical manifestations. Recurrence was confirmed by EEG, MRI, and VGKC-Ab testing.

Previous reports have indicated that VGKC-Ab levels can return to normal spontaneously [5-7]. Patients with negative VGKC-Ab levels may have had previously positive levels at the onset of illness, and it is possible that these antibodies could have been present in some patients but had disappeared by the time the hippocampal sclerosis became clinically evident.

Considering these two possibilities, adult-onset MTLE associated with VGKC-Ab might occur more frequently than expected. According to Sills and Brodie, VGKC-Ab levels were detected in 10% patients with epilepsy at the Epilepsy Unit, Western Infirmary, Glasgow [4]. In cases of unexplained adult-onset MTLE, limbic encephalitis associated with VGKC-Ab should be considered in the differential diagnosis.

Hippocampal swelling reduces with time, while hippocampal high signal intensity and atrophy remain; therefore we cannot distinguish adult-onset MTLE from preexisting hippocampal sclerosis. This condition may improve spontaneously without immunotherapy, and the high VGKC-Ab levels at illness onset can decrease to normal in the chronic phase [5-7]. These points may make diagnosis difficult.

Conclusion

In conclusion, timely diagnosis helps determine if VGKC-Ab is involved in the pathogenesis of MTLE. To investigate the etiology of adult-onset MTLE, serum VGKC-Ab levels should be measured when encephalitic activity is high.
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References

抗Voltage-Gated Potassium Channel複合体抗体関連辺縁系脳炎の関与が考えられた成人発症内側側頭葉てんかんの1例

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要 旨：近年、成人発症内側側頭葉てんかんの一因として抗Voltage-Gated Potassium Channel（VGKC）複合体抗体関連辺縁系脳炎が報告されている。我々は50歳時にてんかん発作を発症した53歳の女性について報告する。発作2か月後に施行された3.0テスラ頭部MRI検査では、フレアー法とT2強調画像にて左海馬高信号および腫脹を認めた。メチルプレドニゾロン経静脈的投与およびカルバマゼピンの経口投与を行い、治療1か月後、頭部MRI検査では左海馬異常所見の改善を認めた。その後てんかん発作を認めていなかったが、初発てんかん発作から3年後の脳波検査ではてんかん発作パターンを認め、頭部MRIにて左海馬高信号、FDG-PETにて同部位の集積亢進を認めた。血清VGKC抗体は118pM（正常値<100 pM）であった。ふたたびメチルプレドニゾロンの経静脈的投与を行った。2か月後には頭部MRI所見は改善し、3か月後にVGKC抗体は4.4 pMまで低下し、てんかん発作も寛解した。本例は中年期に内側側頭葉てんかんを発症しており、その原因として抗VGKC複合体抗体関連辺縁系脳炎と考えられた。原因不明な成人発症内側側頭葉てんかんでは、本例のように免疫学的療法が奏効する抗VGKC複合体抗体関連辺縁系脳炎を鑑別に入れる必要がある。

キーワード：辺縁系脳炎、抗VGKC複合体抗体、成人発症、内側側頭葉てんかん。

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