LETTER TO THE EDITOR

To The Editor

Anti-GM2 Antibodies in Mycoplasma Pneumoniae-Associated Acute Encephalomyelitis

Keywords: Mycoplasma pneumoniae, Acute disseminated encephalomyelitis, Anti-ganglioside antibody, GM2 ganglioside

Acute disseminated encephalomyelitis (ADEM) is a neuroinflammatory disorder associated with antecedent infection, immunization, or vaccination, typically affecting the central nervous system (CNS).[1] ADEM is one of the most severe CNS complications seen in association with Mycoplasma pneumoniae infections.[2,3] Pathogenesis of CNS disease caused by Mycoplasma pneumoniae is incompletely understood but autoimmune phenomena seem to have a major role in the development of ADEM.[2] Anti-GM2 IgM antibodies have been found in patients with chronic motor neuropathy, amyotrophic lateral sclerosis-like disorder after ganglioside therapy, chronic demyelinating neuropathy with sensory ataxia, paraneoplastic polyradiculoneuritis, and Guillain–Barre syndrome (GBS) subsequent to cytomegalovirus infection.[4] We report a case of Mycoplasma pneumoniae-associated ADEM with strongly positive anti-GM2 IgM antibodies.

A previously healthy 22-year-old female developed pain in the head and neck, and nuchal stiffness on the fifth day after upper respiratory tract infection. On the next day, she developed constipation and urinary retention. During the following 3 days, she noticed weakness in the bilateral lower extremities, which progressed to difficulty walking. On the ninth day after upper respiratory tract infection, she was admitted to our hospital. A neurological examination showed paresis in the bilateral lower limbs (Medical Research Council grades in the range of 4/5 proximally, 3/5 distally) and urinary retention. The sensory examination was normal. The tendon reflexes were all brisk, and plantar responses were bilaterally extensor. Catheterization was given for urinary retention.

Serologic tests for cytomegalovirus, parainfluenza virus, influenza A virus, influenza B virus, Coxsackie virus, Epstein–Barr virus, HIV, measles virus, mumps virus, Chlamydia pneumoniae, Borrelia burgdorferi, Legionella pneumophila, Treponema pallidum, and Toxoplasma gondii were negative. Whereas, complement fixation for Mycoplasma pneumoniae IgM antibodies were positive (>1:320). No herpes simplex virus 1 or 2 was detected by polymerase chain reaction testing in cerebrospinal fluid (CSF). Cell count, protein, glucose, and IgG production in CSF were all normal. Oligoclonal bands in CSF and serum were both absent. Anti-AQP4 and anti-MOG IgG antibodies in CSF and serum were both negative. Serum tumor markers including CA199, CA125, NSE, CEA, AFP, and β-HCG were all within normal range. Serum IgG and IgM antibodies against gangliosides by immunoblotting 10 days after admission, including GM1, GM3, GD1a, GD1b, GQ1b, and GT1b were not detected, whereas anti-GM2 IgM antibodies were strongly positive. Other laboratory tests, including complete blood count, urine and stool routine examination, liver and kidney function, ammonia, blood sugar, blood lipid, electrolyte, erythrocyte sedimentation rate, coagulation function, antinuclear, anticytoplasmic, antineuronal, antilupus, and anticardiolipin antibodies, paraneoplastic antibodies, thyroid function and thyroid-related antibodies showed no abnormalities. On the 10th day after upper respiratory tract infection, brain and spinal cord magnetic resonance imaging (MRI) were performed. Multiple high-signal lesions in the brain stem and cervical spinal cord on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequence with slight enhancement after administration of gadolinium were observed (Figure 1). Positron emission tomography-computed tomography of whole body did not prompt malignancy. Nerve conduction study 20 days after onset indicated normal sensory-motor neural response pattern. Visual evoked potentials were also unremarkable.

Mycoplasma pneumoniae-associated ADEM was suspected, and intravenous methylprednisolone 500 mg/day was started for 7 days, during which lower extremities strength markedly improved (Medical Research Council grades in the range of 5/5 proximally, 4+/5 distally). She was then given oral prednisone 60 mg/day, with a decrement of 5 mg/day per week until drug withdrawal. The follow-up MRI on the 50th day after initiation of immunotherapy showed the lesions completely disappeared (Figure 2), and the neurological symptoms resolved thoroughly. Antibody follow-up tests against gangliosides were performed 45 days, 114 days, 591 days, and 1390 days after the first test, respectively, which showed strongly positive anti-GM2 IgM antibodies at the first two tests, borderline at the third test, and negative at the last test. During the follow-up, there was no clinical relapse.

A 22-year-old female developed neurological dysfunction after upper respiratory tract infection, diagnosed as ADEM. Although it mainly affects children, ADEM has been reported in adult patients, and these patients may or may not have encephalopathy.[5] Although the more general term "acute encephalomyelitis" is used in the title, we argue that ADEM quite possibly might refer to everything along an imaging spectrum from subtle, mild hyperintensities (seen in our case) to severe, dense demyelinating hyperintensities.

To the best of our knowledge, this is the first case of Mycoplasma pneumoniae-associated ADEM with strongly positive anti-GM2 antibodies. The temporal association and exclusion of alternative etiologies, such as GBS, multiple sclerosis, spinal arteriovenous malformation, vasculitis, paraneoplastic encephalomyelitis, myopathy, raised the probability of neuroinflammatory disorders related to the antecedent Mycoplasma pneumonia infection. Pathogenesis of CNS disease caused by Mycoplasma pneumoniae is incompletely understood but autoimmune phenomena seem to have a major role in the development of ADEM.[2,3] Molecular mimicry, that is, antigenic similarities between Mycoplasma pneumoniae and human tissues may in part explain this process.[2] Gangliosides constitute a

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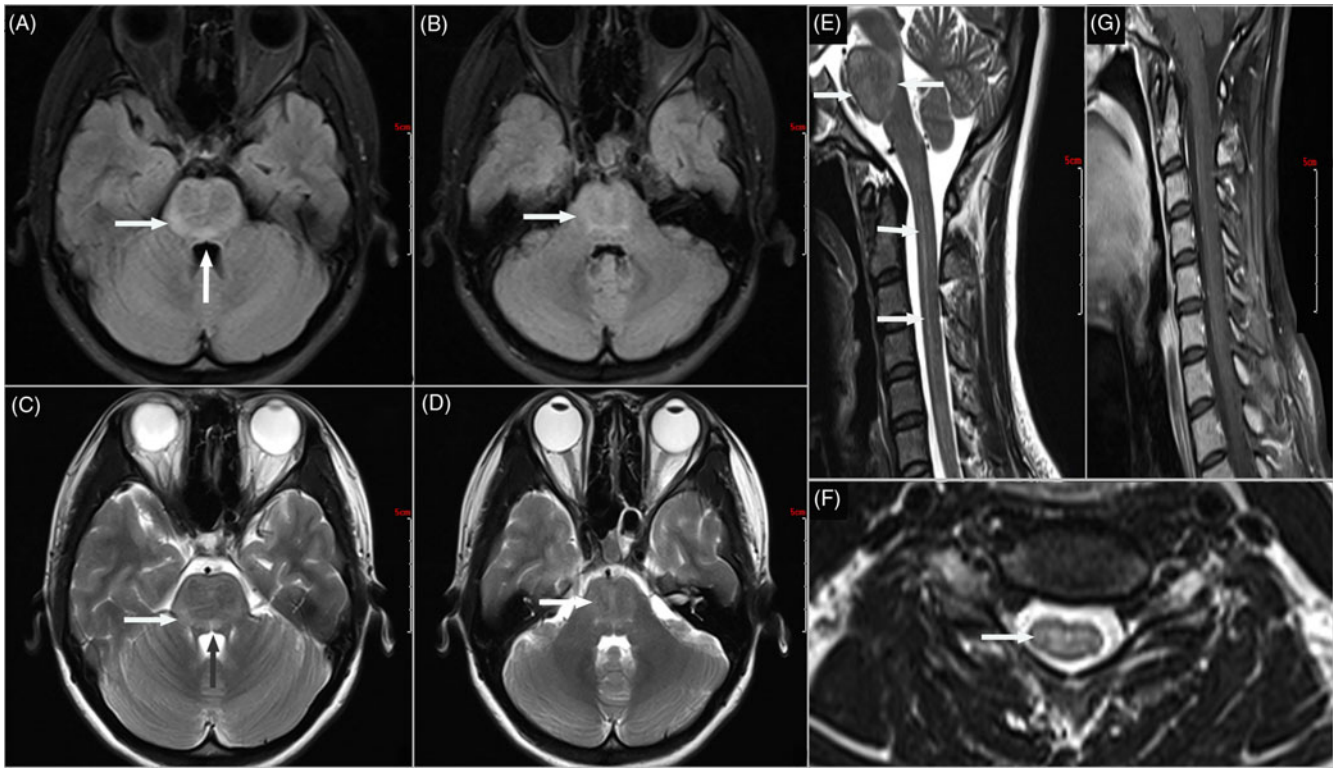

Figure 1: *MR images obtained on the 10th day after upper respiratory tract infection. (A–D) FLAIR and T2-weighted axial brain MR images demonstrated multiple high-signal lesions in the brain stem (indicated by arrows). T2-weighted sagittal (E) and axial (F) cervical spine MR images demonstrated multiple high-signal lesions, which were dominant in the gray matter. (G) The post-contrast T1-weighted sagittal MRI demonstrated pathological enhancement within the cervical cord.*

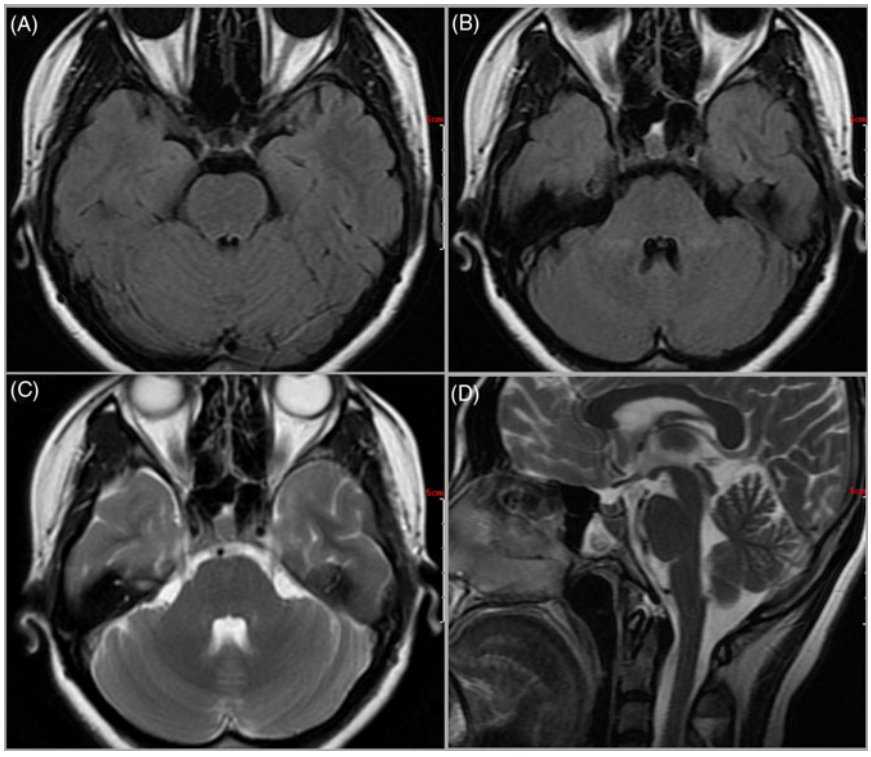

Figure 2: *MR images obtained on the 50th day after initiation of corticosteroids showed the lesions completely disappeared (A–D).*

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large family of glycosphingolipids predominantly distributed on the cell surface membrane and anchored in the external leaflet of the lipid bilayer by a ceramide moiety.[6] Gangliosides, including GM2, are abundantly found not only in the peripheral nervous system, but also in the CNS.[7] The role of anti-GM2 antibodies in the pathophysiology of GBS is now well established,[6] but it remains to be elucidated if they play a similar role in the pathogenesis of CNS inflammatory diseases, for example, ADEM. A case of simultaneous ADEM and GBS with positive anti-GM2 antibodies after H1N1 09 influenza vaccination was previously reported.[8] It could be inferred from our case that there might be a shared epitope among Mycoplasma pneumonia, CNS myelin, and the GM2 ganglioside. Furthermore, anti-GM2 IgM antibodies may play a role in the pathogenesis of Mycoplasma pneumoniae-associated ADEM, which needs further animal experiments to clarify.

Disclosures

The authors report no conflicts of interest.

Statement of authorship

CX designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content. H-SC interpreted the data and revised the manuscript for intellectual content.

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References

1. Kesselring J, Miller DH, Robb SA, et al. Acute disseminated encephalomyelitis. MRI findings and the distinction from multiple sclerosis. Brain 1990;113:291–302.
2. Tsiodras S, Kelesidis T, Kelesidis I, et al. Mycoplasma pneumoniae-associated myelitis: a comprehensive review. Eur J Neurol. 2006;13:112–24.
3. Tsiodras S, Kelesidis I, Kelesidis T, et al. Central nervous system manifestations of Mycoplasma pneumoniae infections. J Infect. 2005;51:343–54.
4. Odaka M, Yuki N. Antibodies to GM2 ganglioside in neurological disorders. Intern Med. 2003;42:220–1.
5. Alper G. Acute disseminated encephalomyelitis. J Child Neurol. 2012;27:1408–25.
6. Yuki N. Guillain-Barré syndrome and anti-ganglioside antibodies: a clinician–scientist's journey. Proc Jpn Acad Ser B Phys Biol Sci. 2012;88:299–326.
7. Schwarz A, Futerman AH. The localization of gangliosides in neurons of the central nervous system: the use of anti-ganglioside antibodies. Biochim Biophys Acta. 1996;1286:247–67.
8. Hoshino T, Uchiyama Y, Ito E, et al. Simultaneous development of acute disseminated encephalomyelitis and Guillain-Barré syndrome associated with H1N1 09 influenza vaccination. Intern Med. 2012;51:1595–8.

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