Commentary: Mycoplasma pneumoniae-associated mild encephalitis/encephalopathy with a reversible splenial lesion: Report of two pediatric cases and a comprehensive literature review

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Article Info

Article Notes
Received: May 15, 2017
Accepted: June 08, 2017

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Keywords
Age
Corpus callosum
Interleukin
MERS
Mycoplasma pneumonia
Race
Reactive oxygen species
Toll-like receptors

ABSTRACT

We previously reviewed clinical characteristics of all reported pediatric cases of Mycoplasma pneumonia (M. pneumoniae)-associated mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). It dominantly occurs in Asian and Caucasian children, suggesting age/race as predisposing factors of MERS. Fever is the most common non-neurological symptom, while more than half of the cases have no respiratory symptoms. Thus, M. pneumoniae-associated MERS may be underestimated and should be a differential diagnosis of febrile children with neurological abnormalities. The mechanism of the disease is unknown. However, susceptibility of immature corpus callosum in young children to immune response-mediated neuroinflammatory stimuli induced by M. pneumoniae, including interleukin-6, reactive oxygen species and toll-like receptors, rather than direct invasion of the organism in central nervous system may contribute to the pathogenesis of MERS. A role of autoantibodies awaits further investigations. Despite excellent prognosis in type I MERS, it remains elusive whether type II MERS is highly associated with neurological sequel.

Introduction

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is clinico-radiologic entity characterized by hyperintense splenium of corpus callosum (SCC) on diffuse-weighted magnetic resonance imaging (MRI). MERS is caused by various etiologies, including infection, intoxication, and vasculitis. Prevalence of MERS was 10.3 % of children with status epilepticus1 and 15.6 % of those with encephalitis in a Japanese nationwide study2. We reviewed clinical characteristics of all reported pediatric cases of Mycoplasma pneumoniae (M. pneumoniae)-associated MERS3. Fever is the most common non-neurological symptom, while more than half of the cases have no respiratory symptoms. Thus, M. pneumoniae-associated MERS may be underestimated and should be a differential diagnosis of children with neurological abnormalities, especially in febrile children with neurological symptoms.

Age/race in M. pneumoniae-associated MERS

As MERS by other etiologies, M. pneumoniae-associated MERS predominantly occurs in children (2-14 years)3. Mean age (8.3 years) of children with M. pneumoniae-associated MERS3 is similar to that (8.7 years) of those with M. pneumoniae-associated encephalitis4, suggesting that age-related immune dysfunction may predispose to MERS. Childhood M. pneumoniae infection is complicated by different host-dependent characteristics; variable persistence of antibodies, missing IgM response after re-infection and infrequent production
of IgA antibodies. M. pneumoniae infection is less prevalent in infants in whom symptoms are milder, while it predominantly occurs in children (5-15 years). In animals with deleted thymus-dependent lymphocytes, M. pneumoniae infection caused less severe pneumonic lesions than infected immunologically competent animals. In vivo study showed that M. pneumoniae-induced pulmonary inflammation was more severe after second infection than that after primary infection. In humans, lymphocytes had a memory of previous M. pneumoniae infection for a long time (≤10 years). Thus, more marked inflammation may occur after second M. pneumoniae infection. This may explain why M. pneumoniae infection predominantly occurs in children and suggests that clinical manifestations and extrapulmonary complications of M. pneumoniae infection are caused by immunopathologic response rather than the organism itself.

As MERS by other causes, M. pneumoniae-associated MERS exclusively occurs in Asian and Caucasian patients. Acute disseminated encephalomyelitis caused less prevalent CC involvement in Asian than in American patients. MERS occurred in Japanese twins and sisters. These findings suggest genetic predisposing factor to MERS.

Premature SCC and MERS

CC is premature until 6–8 years of age at which myelination is complete. SCC matures between 4 and 18 years of age. The age effect on maturation is stronger in SCC than in other callosal subregions. No sex difference is found in maturation during the development except infancy (0-24 months), in whom the SCC size is greater in females. Maturation of CC is correlated with age, and age at which the CC is immature corresponds to the prevalent age of MERS children. Premature oligodendrocytes contained less antioxidants and anti-apoptotic Bcl-2 but higher apoptotic Bax than matured cells, being more susceptible to environmental stress including oxidant stress. In response to demyelinating stimulus, demyelination was more severe in the CC of juvenile and young-adult mice than in middle-aged mice. Sirtuin 3 (Sirt3), which reduces ROS by deacetylating forkhead box O3a that transactivates antioxidant genes, was localized in the ameboid microglial cells and distributed in the CC of the early postnatal rats, and diminished in the ramified microglial cells of the CC in the adult rats. Thus, premature CC may be more susceptible to neuroinflammation, and this may account for prevalence of MERS in children.

SCC is posterior part of the CC, connecting different cortical areas, including occipital, parietal and temporal lobes. The lesions in the SCC (type I MERS) and other brain regions connecting the SCC (type II MERS) result in various neurological manifestations. Hyperintensity of the SCC on diffusion-weighted MRI may represent intramyelinic edema due to inflammation, interstitial edema in tightly packed fibers, and a transient migration of inflammatory cells in the CC.

Mechanism of MERS

As MERS by other etiologies, the organism was not detected in cerebrospinal fluid (CSF) of the majority of patients with M. pneumoniae-associated MERS, suggesting that systemic factors rather than direct invasion of the organism in central nervous system may play a pathogenic role for MERS. Since SCC receives arterial supply from the vertebrobasilar system, factors in serum/CSF may affect its function. Hyponatremia is proposed as a possible cause of MERS. Since it occurred in only 31.0% -60.0% of MERS cases although high prevalence (83.3 %) was reported, hyponatremia may be a predisposing but not causative factor: Electrolyte-water imbalance by arginine vasopressin suppression is proposed as a cause, but this awaits further investigations.

Lipid-associated membrane proteins from M. pneumoniae produce proinflammatory cytokines such as interleukin (IL)-6 and ROS in pulmonary epithelial cells and monocytes. Serum levels of IL-6 and tumor necrosis factor (TNF)-α were increased in children with M. pneumoniae infection. These factors enhance permeability of blood-brain barrier, resulting in neuroinflammation, which renders microglia in the CC release proinflammatory cytokines and ROS. In fact, the levels of IL-6 were increased in cerebrospinal fluid (CSF) of children with MERS due to M. pneumoniae, Enterococcus faecalis, and influenza and M. pneumoniae-associated encephalitis. Oxidative stress marker was found in CSF of MERS by other etiologies. Expression of heparan sulphate proteoglycan, syndecan-2, in microglial cells of the CC was increased in response to hypoxia, which is associated with seizure. Increased Sdc-2 expression enhanced the release of proinflammatory cytokines (e.g. TNF-α and IL-1β) and ROS in microglial cells. Transgenic mice with astrocyte-targeted production of IL-6 showed inefficient removal of demyelinating stimulus-induced degraded myelin and axonal protection in the CC compared to wild type mice, suggesting that IL-6 may impair myelin maintenance and induce axonal injury. In children infected with M. pneumoniae, toll-like receptor (TLR)2 and TLR4, which are expressed in the CC, were increased. TLR4 expression in the CC in neonatal microglia was markedly enhanced in response to hypoxia. In vivo study showed that TLRs in the CC increased the levels of proinflammatory cytokines (IL-6, IL-1β, and TNF-α), leading to neuroinflammation via mitogen-activated protein kinase and NF-kB pathways. Knockdown of TLR2 in mice attenuated cortical apoptosis, lessened glial response, and reduced the secondary axonal and neuronal injury in the cortex by inhibiting these pathways.
The CC contains glutamate receptors\textsuperscript{35}, N-methyl-D-aspartate receptor (NMDAR)\textsuperscript{46} and voltage-gated potassium channel (VGKC)\textsuperscript{57}. Pediatric case of MERS with anti-glutamate ε2 receptor (GluRe2) antibody\textsuperscript{48} and adult case with anti-VGKC antibody\textsuperscript{49} were reported. These antibodies may disturb neuronal signaling by inhibiting the receptor/channel-mediated signaling in the CC\textsuperscript{59}. Adult case of autoimmune encephalitis with anti-GluRe2 antibody showed severe neurological findings, and hyperintensity in frontal/parietal cortices on MR\textsuperscript{51}. These data suggest that encephalitis due to autoimmune antibodies may have a wide range of clinical characteristics, MRI findings, and outcome.

Recently, anti-NMDAR encephalitis, best characterized autoimmune encephalitis, has been reported\textsuperscript{52-54}. It is different from MERS because of positive anti-NMDAR antibody in serum/CSF, severe clinical symptoms, older age (>12 years), female prevalence, tumor association, MRI findings (brain regions other than CC and infrequently spinal cord), relatively worse outcome (4% mortality), recurrence of the disease, and need for immunosuppressive therapy and long hospitalization\textsuperscript{52}. Some of the patients with anti-NMDAR encephalitis were associated with infection, including \textit{M. pneumoniae}\textsuperscript{52}. Anti-VGKC antibody or anti-NMDAR antibody or both were found in children with \textit{M. pneumoniae}-associated encephalitis\textsuperscript{54}, suggesting that anti-VGKC-complex antibody and anti-NMDAR antibody could be induced as part of the immune response to \textit{M. pneumoniae}. In anti-NMDAR encephalitis, antibody titers in CSF, and to a lesser extent in serum, were correlated with clinical outcome\textsuperscript{53}. Since prognosis of MERS is excellent, anti-NMDAR antibody has not been measured in MERS patients. If routine measurement could detect anti-NMDAR antibody, such cases of MERS may be considered subtype of autoimmune encephalitis with mild clinical symptoms and excellent outcome, as previously discussed about MERS\textsuperscript{48} and autoimmune encephalitis\textsuperscript{52} with anti-GluRe2 antibody. This hypothesis awaits further investigations.

### Type II MERS, macrolide resistance, and a risk of neurological sequel in \textit{M. pneumoniae}-associated MERS

Despite excellent prognosis of type I MERS, regardless of etiologies, type II MERS due to \textit{M. pneumoniae} infection\textsuperscript{5,35} and other etiologies\textsuperscript{56} may develop neurological sequel. Although macrolide-resistant \textit{M. pneumoniae} infection increased a risk of encephalitis\textsuperscript{57}, it does not appear to increase a risk of MERS\textsuperscript{3}. No valuable therapy is established for \textit{M. pneumoniae}-associated MERS\textsuperscript{1,20}.

### Future perspectives

A lack of enough data warrants further investigations to clarify clinical characteristics and mechanisms, including potential role of autoantibodies, in MERS due to \textit{M. pneumoniae} and other etiologies.

**References**


