

Commentary

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

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ABSTRACT

We previously reviewed clinical characteristics of all reported pediatric cases of Mycoplasma pneumoniae (*M.pneumoniae*)-associated mild encephalitis/encephalopathy with a reversible splenic 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 splenic lesion (MERS) is clinico-radiologic entity characterized by hyperintense splenic 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 antibodies⁵. *M. pneumoniae* infection is less prevalent in infants in whom symptoms are milder⁶, while it predominantly occurs in children (5-15 years)⁷. In animals with deleted thymus-dependent lymphocytes, *M.pneumoniae* infection caused less severe pneumonic lesions than infected immunologically competent animals⁸. In vivo study showed that *M.pneumoniae*-induced pulmonary inflammation was more severe after second infection than that after primary infection⁹. In humans, lymphocytes had a memory of previous *M.pneumoniae* infection for a long time (≤ 10 years)¹⁰. 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 itself⁵.

As MERS by other causes, *M.pneumoniae*-associated MERS exclusively occurs in Asian and Caucasian patients³. Acute disseminated encephalomyelitis caused less prevalent CC involvement in Asian than in American patients¹¹. MERS occurred in Japanese twins¹² and sisters¹³. 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 complete¹⁴. SCC matures between 4 and 18 years of age^{15,16}. The age effect on maturation is stronger in SCC than in other callosal subregions¹⁶. No sex difference is found in maturation during the development except infancy (0-24 months), in whom the SCC size is greater in females¹⁵. Maturation of CC is correlated with age¹⁷, 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 stress¹⁸⁻²⁰. In response to demyelinating stimulus, demyelination was more severe in the CC of juvenile and young-adult mice than in middle-aged mice²¹. Sirtuin 3 (Sirt3), which reduces ROS by deacetylating forkhead box O3a that transactivates antioxidant genes, was localized in the amoeboid 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 rats²². 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 lobes²³. The lesions in the SCC (type I MERS) and other brain regions connecting the SCC (type II MERS) result in various neurological manifestations²⁴. 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 CC²⁵.

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 MERS³, 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 system²⁶, factors in serum/CSF may affect its function. Hyponatremia is proposed as a possible cause of MERS²⁵. Since it occurred in only 31.0% -60.0%^{3,27,28} of MERS cases although high prevalence (83.3 %) was reported²⁵, hyponatremia may be a predisposing but not causative factor. Electrolyte-water imbalance²⁵ by arginine vasopressin suppression²⁹ 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 cells³⁰ and monocytes³¹. Serum levels of IL-6 and tumor necrosis factor (TNF)- α were increased in children with *M.pneumoniae* infection³². These factors enhance permeability of blood-brain barrier³³, 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*³⁴, *Enterococcus faecalis*³⁵, and influenza³⁶ and *M.pneumoniae*-associated encephalitis³⁷. Oxidative stress marker was found in CSF of MERS by other etiologies³⁸. Expression of heparan sulphate proteoglycan, syndecan-2 (Sdc-2), in microglial cells of the CC was increased in response to hypoxia³⁹, which is associated with seizure⁴⁰. Increased Sdc-2 expression enhanced the release of proinflammatory cytokines (e.g. TNF- α and IL-1 β) and ROS in microglial cells⁴⁰. 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 mice⁴¹, suggesting that IL-6 may impair myelin maintenance and induce axonal injury. In children infected with *M.pneumoniae*, toll-like receptor (TRL)2 and TRL4, which are expressed in the CC^{42,43}, were increased⁴⁴. TLR4 expression in the CC in neonatal microglia was markedly enhanced in response to hypoxia⁴². In vivo study showed that TLRs in the CC increased the levels of proinflammatory cytokines (IL-6, IL-1 β , and TNF- α), leading to neuroinflammation via mitogen-activated protein kinase and NF- κ B pathways⁴³. 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 pathways⁴³.

The CC contains glutamate receptors⁴⁵, N-methyl-D-aspartate receptor (NMDAR)⁴⁶ and voltage-gated potassium channel (VGKC)⁴⁷. Pediatric case of MERS with anti-glutamate $\epsilon 2$ receptor (GluR $\epsilon 2$) antibody⁴⁸ and adult case with anti-VGKC antibody⁴⁹ were reported. These antibodies may disturb neuronal signaling by inhibiting the receptor/channel-mediated signaling in the CC⁵⁰. Adult case of autoimmune encephalitis with anti-GluR $\epsilon 2$ antibody showed severe neurological findings, and hyperintensity in frontal/parietal cortices on MRI⁵¹. 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 reported⁵²⁻⁵⁴. 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 hospitalization⁵². Some of the patients with anti-NMDAR encephalitis were associated with infection, including *M.pneumoniae*⁵². Anti-VGKC antibody or anti-NMDAR antibody or both were found in children with *M.pneumoniae*-associated encephalitis⁵⁴, suggesting that anti-VGKC-complex antibody and anti-NMDAR antibody could be induced as part of the immune response to *M.pneumoniae*. In anti-NMDAR encephalitis, antibody titers in CSF, and to a lesser extent in serum, were correlated with clinical outcome⁵³. 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 MERS⁴⁸ and autoimmune encephalitis⁵¹ with anti-GluR $\epsilon 2$ antibody. This hypothesis awaits further investigations.

Type II MERS, macrolide resistance, and a risk of neurological sequel in *M.pneumoniae*-associated MERS

Despite excellent prognosis of type I MERS, regardless of etiologies, type II MERS due to *M.pneumoniae* infection^{3,55} and other etiologies⁵⁶ may develop neurological sequel. Although macrolide-resistant *M.pneumoniae* infection increased a risk of encephalitis⁵⁷, it does not appear to increase a risk of MERS³. No valuable therapy is established for *M.pneumoniae*-associated MERS^{3,28}.

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 *M.pneumoniae* and other etiologies.

References

- Oguri M, Saito Y, Fukuda C, et al. Distinguishing acute encephalopathy with biphasic seizures and late reduced diffusion from prolonged febrile seizures by acute phase EEG spectrum analysis. *Yonago Acta Med.* 2016; 59(1): 1-14.
- Hoshino A, Saitoh M, Oka A, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. *Brain Dev.* 2012; 34(5): 337-43.
- Ueda N, Minami S, Akimoto M. Mycoplasma pneumoniae-associated mild encephalitis/encephalopathy with a reversible splenic lesion: report of two pediatric cases and a comprehensive literature review. *BMC Infect Dis.* 2016; 16: 671.
- Meyer Sauteur PM, Moeller A, Rely C, et al. Swiss Pediatric Surveillance Unit (SPSU). Swiss national prospective surveillance of paediatric Mycoplasma pneumoniae-associated encephalitis. *Swiss Med Wkly.* 2016; 146: w14222.
- Atkinson TP, Balish MF, Waites KB. Epidemiology, clinical manifestations, pathogenesis and laboratory detection of Mycoplasma pneumoniae infections. *FEMS Microbiol Rev.* 2008; 32(6): 956-73.
- Sun H, Chen Z, Yan Y, et al. Epidemiology and clinical profiles of Mycoplasma pneumoniae infection in hospitalized infants younger than one year. *Respir Med.* 2015; 109(6): 751-7.
- Meyer Sauteur PM, Unger WW, Nadal D, et al. Infection with and carriage of Mycoplasma pneumoniae in children. *Front Microbiol.* 2016; 7: 329.
- Taylor G, Taylor-Robinson D. The part played by cell-mediated immunity in mycoplasma respiratory infections. *Dev Biol Stand.* 1975; 28: 195-210.
- Kurai D, Nakagaki K, Wada H, et al. Mycoplasma pneumoniae extract induces an IL-17-associated inflammatory reaction in murine lung: implication for mycoplasmal pneumonia. *Inflammation.* 2013; 36(2): 285-93.
- Biberfeld G, Biberfeld P, Sterner G. Cell-mediated immune response following Mycoplasma pneumoniae infection in man. I. Lymphocyte stimulation. *Clin Exp Immunol.* 1974; 17(1): 29-41.
- Koelman DL, Benkeser DC, Xu Y, et al. Acute disseminated encephalomyelitis in China, Singapore and Japan: a comparison with the USA. *Eur J Neurol.* 2017; 24(2): 391-6.
- Tahara J, Shinozuka J, Awaguni H, et al. Mild encephalopathy with reversible lesions in the splenium of corpus callosum and bilateral cerebral deep white matter in identical twins. *Pediatr Rep.* 2016; 8(3): 6615.
- Imamura T, Takanashi J, Yasugi J, et al. Sisters with clinically mild encephalopathy with a reversible splenic lesion (MERS)-like features; Familial MERS? *J Neurol Sci.* 2010; 290(1-2): 153-6.
- Takeuchi N, Oouchida Y, Izumi S. Motor control and neural plasticity through interhemispheric interactions. *Neural Plast.* 2012; 2012: 823285.
- Vannucci RC, Barron TF, Vannucci SJ. Development of the corpus callosum: An MRI study. *Dev Neurosci.* 2016 Dec 24. doi: 10.1159/000453031.
- Westerhausen R, Fjell AM, Krogstad SK, et al. Selective increase in posterior corpus callosum thickness between the age of 4 and 11 years. *Neuroimage.* 2016; 139: 17-25.
- Takeda S, Hirashima Y, Ikeda H, et al. Determination of indices of the corpus callosum associated with normal aging in Japanese individuals. *Neuroradiology.* 2003; 45(8): 513-8.
- Butts BD, Houde C, Mehmet H. Maturation-dependent sensitivity of oligodendrocyte lineage cells to apoptosis: implications for normal development and disease. *Cell Death Differ.* 2008; 15(7): 1178-86.

19. Baud O, Greene AE, Li J, et al. Glutathione peroxidase-catalase cooperativity is required for resistance to hydrogen peroxide by mature rat oligodendrocytes. *J Neurosci*. 2004; 24(7): 1531-40.
20. Bernardo A, Greco A, Levi G, et al. Differential lipid peroxidation, Mn superoxide, and bcl-2 expression contribute to the maturation-dependent vulnerability of oligodendrocytes to oxidative stress. *J Neuropathol Exp Neurol*. 2003; 62(5): 509-19.
21. Wang H, Li C, Wang H, et al. Cuprizone-induced demyelination in mice: age-related vulnerability and exploratory behavior deficit. *Neurosci Bull*. 2013; 29(2): 251-9.
22. Rangarajan P, Karthikeyan A, Lu J, et al. Sirtuin 3 regulates Foxo3a-mediated antioxidant pathway in microglia. *Neuroscience*. 2015; 311: 398-414.
23. Van der Knaap LJ, Van der Ham IJ. How does the corpus callosum mediate interhemispheric transfer? A review. *Behav Brain Res*. 2011; 223(1): 211-21.
24. Gallucci M, Limbucci N, Paonessa A, et al. Reversible focal splenial lesions. *Neuroradiology*. 2007; 49(7): 541-4.
25. Takanashi J, Tada H, Maeda M, et al. Encephalopathy with a reversible splenial lesion is associated with hyponatremia. *Brain Dev*. 2009; 31(3): 217-20.
26. Kakou M, Velut S, Destrieux C. [Arterial and venous vascularization of the corpus callosum]. *Neurochirurgie*. 1998;44(1 Suppl):31-7. [in French]
27. Pan JJ, Zhao YY, Lu C, et al. Mild encephalitis/encephalopathy with a reversible splenial lesion: five cases and a literature review. *Neurol Sci*. 2015; 36(11): 2043-51.
28. Fang Q, Chen L, Chen Q, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion of corpus callosum in Chinese children. *Brain Dev*. 2017; 39(4): 321-6.
29. Prilipko O, Delavelle J, Lazeyras F, et al. Reversible cytotoxic edema in the splenium of the corpus callosum related to antiepileptic treatment: report of two cases and literature review. *Epilepsia*. 2005; 46(10): 1633-6.
30. Choi SY, Lim JW, Shimizu T, et al. Reactive oxygen species mediate Jak2/Stat3 activation and IL-8 expression in pulmonary epithelial cells stimulated with lipid-associated membrane proteins from *Mycoplasma pneumoniae*. *Inflamm Res*. 2012; 61(5): 493-501.
31. Hu J, Chen C, Ou G, et al. Nrf2 regulates the inflammatory response, including heme oxygenase-1 induction, by *Mycoplasma pneumoniae* lipid-associated membrane proteins in THP-1 cells. *Pathog Dis*. 2017; 75(4). doi: 10.1093/femspd/ftx044.
32. Zhao JL, Wang X, Wang YS. Relationships between Th1/Th2 cytokine profiles and chest radiographic manifestations in childhood *Mycoplasma pneumoniae* pneumonia. *Ther Clin Risk Manag*. 2016; 12: 1683-92.
33. Rochfort KD, Collins LE, McLoughlin A, et al. Tumour necrosis factor- α -mediated disruption of cerebrovascular endothelial barrier integrity in vitro involves the production of proinflammatory interleukin-6. *J Neurochem*. 2016; 136(3): 564-72.
34. Yuan ZF, Shen J, Mao SS, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion associated with *Mycoplasma pneumoniae* infection. *BMC Infect Dis*. 2016; 16: 230.
35. Kometani H, Kawatani M, Ohta G, et al. Marked elevation of interleukin-6 in mild encephalopathy with a reversible splenial lesion (MERS) associated with acute focal bacterial nephritis caused by *Enterococcus faecalis*. *Brain Dev*. 2014; 36(6): 551-3.
36. Morichi S, Kawashima H, Ioi H, et al. High production of interleukin-10 and interferon- γ in influenza-associated MERS in the early phase. *Pediatr Int*. 2012; 54(4): 536-8.
37. Narita M, Tanaka H, Togashi T, et al. Cytokines involved in CNS manifestations caused by *Mycoplasma pneumoniae*. *Pediatr Neurol*. 2005; 33(2): 105-9.
38. Miyata R, Tanuma N, Hayashi M, et al. Oxidative stress in patients with clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). *Brain Dev*. 2012; 34(2): 124-7.
39. Kaur C, Sivakumar V, Yip GW, et al. Expression of syndecan-2 in the amoeboid microglial cells and its involvement in inflammation in the hypoxic developing brain. *Glia*. 2009; 57(3): 336-49.
40. Wei Y, Ullah G, Ingram J, et al. Oxygen and seizure dynamics: II. Computational modeling. *J Neurophysiol*. 2014; 112(2): 213-23.
41. Petković F, Campbell IL, Gonzalez B, et al. Astrocyte-targeted production of interleukin-6 reduces astroglial and microglial activation in the cuprizone demyelination model: Implications for myelin clearance and oligodendrocyte maturation. *Glia*. 2016; 64(12): 2104-19.
42. Yao L, Kan EM, Lu J, et al. Toll-like receptor 4 mediates microglial activation and production of inflammatory mediators in neonatal rat brain following hypoxia: role of TLR4 in hypoxic microglia. *J Neuroinflammation*. 2013; 10: 23.
43. Zhao Y, Zhao J, Zhang M, et al. Involvement of toll like receptor 2 signaling in secondary injury during experimental diffuse axonal injury in rats. *Mediators Inflamm*. 2017; 2017: 1570917.
44. Fan Q, Gu T, Li P, et al. Roles of T-cell immunoglobulin and mucin domain genes and toll-like receptors in wheezy children with *Mycoplasma pneumoniae* pneumonia. *Heart Lung Circ*. 2016; 25(12): 1226-31.
45. Azami Tameh A, Clarner T, Beyer C, et al. Regional regulation of glutamate signaling during cuprizone-induced demyelination in the brain. *Ann Anat*. 2013; 195(5): 415-23.
46. Zhang J, Liu J, Fox HS, et al. N-methyl-D-aspartate receptor-mediated axonal injury in adult rat corpus callosum. *J Neurosci Res*. 2013; 91(2): 240-8.
47. Huang CY, Chu D, Hwang WC, et al. Coexpression of high-voltage-activated ion channels Kv3.4 and Cav1.2 in pioneer axons during pathfinding in the developing rat forebrain. *J Comp Neurol*. 2012; 520(16): 3650-72.
48. Fujiki Y, Nakajima H, Ito T, et al. A case of clinically mild encephalitis/encephalopathy with a reversible splenial lesion associated with anti-glutamate receptor antibody. *Rinsho Shinkeigaku*. 2011; 51(7): 510-3. [in Japanese]
49. Gilder TR, Hawley JS, Theeler BJ. Association of reversible splenial lesion syndrome (RESLES) with anti-VGKC autoantibody syndrome: a case report. *Neurol Sci*. 2016; 37(5): 817-9.
50. Spitzer S, Volbracht K, Lundgaard I, et al. Glutamate signalling: A multifaceted modulator of oligodendrocyte lineage cells in health and disease. *Neuropharmacology*. 2016; 110(Pt B): 574-85.
51. Hayata Y, Hamada K, Sakurai Y, et al. Anti-glutamate $\epsilon 2$ receptor antibody-positive and anti-N-methyl-d-aspartate receptor antibody-negative lobar encephalitis presenting as global aphasia and swallowing apraxia. *Case Rep Neurol*. 2014; 6(3): 291-6.
52. Dalmau J, Lancaster E, Martinez Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011; 10(1): 63-74.
53. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titers at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*. 2014; 13(2): 167-77.
54. Pillai SC, Hachohen Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics*. 2015; 135(4): e974-84.

55. Notebaert A, Willems J, Coucke L, et al. Expanding the spectrum of MERS type 2 lesions, a particular form of encephalitis. *Pediatr Neurol.* 2013; 48(2): 135-8.
56. Chen WX, Liu HS, Yang SD, et al. Reversible splenial lesion syndrome in children: Retrospective study and summary of case series. *Brain Dev.* 2016; 38(10): 915-27.
57. Zhou Y, Zhang Y, Sheng Y, et al. More complications occur in macrolide-resistant than in macrolide-sensitive *Mycoplasma pneumoniae* pneumonia. *Antimicrob Agents Chemother.* 2014; 58(2): 1034-8.