SEROPOSITIVE LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS FOLLOWING UNILATERAL PNEUMONIA

Seropozytywne poprzeczne zapalenie rdzenia kręgowego w następstwie jednostronnego zapalenia płuc

Franciszek Ługowski, Julia Babińska

Faculty of Medicine, Medical University of Warsaw, Poland

Franciszek Ługowski – 0000-0001-6952-4927
Julia Babińska – 00009-0003-8759-7806

Abstract

Longitudinal extensive transverse myelitis is an exceedingly rare condition with several known triggering factors, both viral and bacterial. While it has been widely associated with COVID-19, it can also occur following pneumonia caused by other agents. The underlying mechanism can include aquaporin-4 antibodies (AQP4-Ab). It causes major neurological manifestations and poses a life-threatening risk, particularly by affecting respiratory muscles. This case report delineates longitudinal extensive transverse myelitis following unilateral pneumonia, associated with AQP4-Ab, in a 62-year-old woman who experienced abdominal pain, a gradual loss of sensation in the extremities, and eventual inability to walk with a total loss of sensation. Her spinal MRI revealed increased T2 signal, consistent with longitudinal extensive transverse myelitis. AQP4-ab antibodies were present. Treatment with methylprednisolone led to symptom improvement. Protein levels in the cerebrospinal fluid were also analyzed. Our findings suggest a potential difference in protein levels in cerebrospinal fluid between bacterial and viral longitudinal extensive transverse myelitis. Magnetic resonance imaging is the primary method of diagnosis and can help exclude other possible etiologies of neurological symptoms. When managing longitudinal extensive transverse myelitis, timing is critical to prevent paralysis of the respiratory muscles. Although extremely rare, longitudinal extensive transverse myelitis can have diverse origins as well as clinical manifestations, and its management continues to present a significant challenge.

Streszczenie

Poprzeczne zapalenie rdzenia kręgowego jest niezwykle rzadką jednostką chorobową, z kilkoma znanymi czynnikami wyzwalającymi – zarówno wirusowymi, jak i bakteryjnymi. Powszechnie wiąże się ją z COVID-19, jednakże może występować po zapaleniu płuc spowodowanym innymi czynnikami. Podstawowy mechanizm może obejmować przeciwciała przeciwko akwaporynom-4 (AQP4-Ab). Choroba ta wywołuje istotne objawy neurologiczne i poprzez uszkodzenie mięśni oddechowych powoduje poważne zagrożenie życia. W pracy opisano przypadek poprzecznego zapalenie rdzenia kręgowego po jednostronnym zapaleniu płuc związanym z AQP4-Ab u 62-letniej kobiety, u której wystąpiły bóle brzucha, stopniowa utrata czucia w kończynach, a następnie niezdolność do chodzenia, z całkowitą utratą czucia. Badanie MRI kręgosłupa wykazało zwiększony sygnał T2, zgodny z poprzecznym zapaleniem rdzenia kręgowego. Stwierdzono obecność AQP4-ab. Leczenie metyloprednizolonem przyniosło poprawę w zakresie objawów. Stężenie białka w płynie mózgowo-rdzeniowym sugeruje potencjalne różnice między wirusowym a bakteryjnym poprzecznym zapaleniem rdzenia kręgowego. Obrazowanie MRI jest podstawową metodą diagnostyczną, umożliwiającą wykluczenie innych możliwych przyczyn objawów neurologicznych. Podczas leczenia kluczowe jest odpowiednie czasowe działanie w celu zapobieżenia paraliżowi mięśni oddechowych. Poprzeczne zapalenie rdzenia kręgowego pozostaje nadal niezwykle rzadkim schorzeniem, które może mieć różne pochodzenie oraz manifestacje kliniczne, a jego leczenie pozostaje istotnym wyzwaniem.

Keywords: neuromyelitis optica; neuroimmunology; longitudinally extensive transverse myelitis; LETM

Słowa kluczowe: *neuromyelitis optica;* neuroimmunologia; poprzeczne porażenie rdzenia; LETM

DOI 10.53301/lw/190392

Received: 17.06.2024

Accepted: 24.06.2024

Corresponding author:
Franciszek Ługowski
Faculty of Medicine, Medical University of Warsaw,
24c Kuropatwy Str., 02-892 Warsaw
e-mail: franciszeklugowski@gmail.com

Introduction

Longitudinal extensive transverse myelitis (LETM) is a type of spinal cord lesion spanning at least three vertebrae, leading to significant neurological impairment [1]. LETM is often associated with a neuromyelitis optica spectrum disease (NMO-SD) [2]. The condition is related to a severe autoimmune response. It can accompany various diseases including multiple sclerosis and systemic lupus erythematosus. Moreover, LETM can occur as a result of various infections, such as Mycobacterium tuberculosis [3]. However, there are considerably fewer cases of para-/post-bacterial LETM in comparison with viral infections. Mycoplasma is a known causative agent for LETM associated with pneumonia, with neurological complications observed in 0.01% to 4.8% of patients [4]. There is significant evidence suggesting the role of viruses in central nervous system (CNS) invasion, leading to neurological symptoms, including coronaviruses [5, 6]. While coronaviruses are primarily recognized for causing respiratory and enteric infections, often mild or even asymptomatic, they have also been identified as potential triggers for transverse myelitis (TM) [7]. There have also been numerous reports of LETM occurring after COVID-19 vaccination [8]. The most distinctive marker of LETM, as well as NMO-SD, are aquaporin-4-antibodies (AQP4-Ab) [9]. Aquaporin 4 (AQP4) is a water channel targeted by immunoglobulin G autoantibodies in NMO-SD. AQP4 is expressed in the foot processes of astrocytes in the CNS, as well as in skeletal muscle and epithelial cells in the kidney, lung, and gastrointestinal organs. It plays a significant role in the movement of water into and out of the brain, migration of astrocytes, glial scar formation, and neuroexcitatory processes. AQP4 monomers assemble into tetramers in membranes, which then aggregate to form orthogonal arrays. The pathogenic mechanism involving AQP-Ab in NMO-SD includes complement- and cell-mediated astrocyte cytotoxicity, which leads to an inflammatory response with damage to oligodendrocytes and demyelination [10]. However, AQP4-Ab are not present in every patient. According to a study conducted in the United Kingdom, they occur in approximately 58% of cases [11]. Here, we report a rare case of rapid-onset LETM with the presence of AQP4-Ab, which occurred shortly after symptoms of bacterial pneumonia.

Case report

A 62-year-old woman was admitted to our hospital with acute girdle pain in the abdomen, radiating to the lumbar region, rated as 10/10 on the NRS scale, in October 2023. The patient reported general malaise, weight loss of five kilograms, and pyrexia. The pain had persisted for four days and worsened on breathing. The patient had not moved her bowels for two days. On examination, no peritoneal symptoms were found. Ultrasonography of the abdomen showed a 41-mm cyst in the left kidney, while the rest of the findings were unremarkable. Four days before admission, urinalysis, conducted at another hospital, revealed a urinary tract infection (UTI). Ciprofloxacin was administered orally. On admission, the patient presented no signs of UTI, and she tested negative for COVID-19. During hospitalization, she developed pneumonia, presenting with fever, moderate dyspnea, and fatigue. On auscultation, respiratory sounds were muted over the base of the left lung. A chest X-ray showed no signs of pneumothorax or fluid, but a 35-mm limited area of density in the lower lobe of the left lung, along with tubercular lesions and pleural nodules in the upper lobe of the left lung. High-resolution computed tomography of the thorax revealed plates of atelectasis and signs of pneumonia in the lower lobe of the left lung, with parenchymal densities near the interlobar fissure. Smaller subpleural areas of density were found in segments 1 + 2 and 6 of the left lung. An air bronchogram confirmed inflammation. Blood tests showed the following results: procalcitonin: 0.11 ng/ml, C-reactive protein: 153 mg/l, while other markers were normal. A blood culture was taken. The patient was started on intravenous ceftriaxone and metronidazole. Later that evening, the patient began to feel muscle numbness that progressed to difficulty walking. She denied pain but reported symmetrical paresthesia in the lower extremities. The following day, the patient was unable to walk. Moreover, hiccups and vomiting ensued. She vomited once or twice a day over the next three days. On physical examination, paresis of all muscle groups in the lower extremities, with no superficial sensation, was diagnosed. The patient denied any prior trauma or accident. A neurological consultation was sought, with LETM, meningitis, systemic lupus erythematosus (SLE), or syphilis suspected. The differential diagnosis included vitamin B_{12} deficiency ANA, ANCA, Borrelia, and WR, all of which were negative. The manifestations progressed the following day, as the patient reported loss of control over urinary sphincters. MRI of the vertebral column (C-Th-LS) revealed signs of LETM (Fig. 1). Blood was taken to assess AQP4-Ab and anti-Myelin Oligodendrocyte Glycoprotein antibodies (anti-MOG) in the serum. AQP4-Ab antibodies were detected at a titer of 1:640. A glycemic profile was also established. The following medications were administered:1 g of methylprednisolone i.v., low-molecular-weight heparin, and proton pump

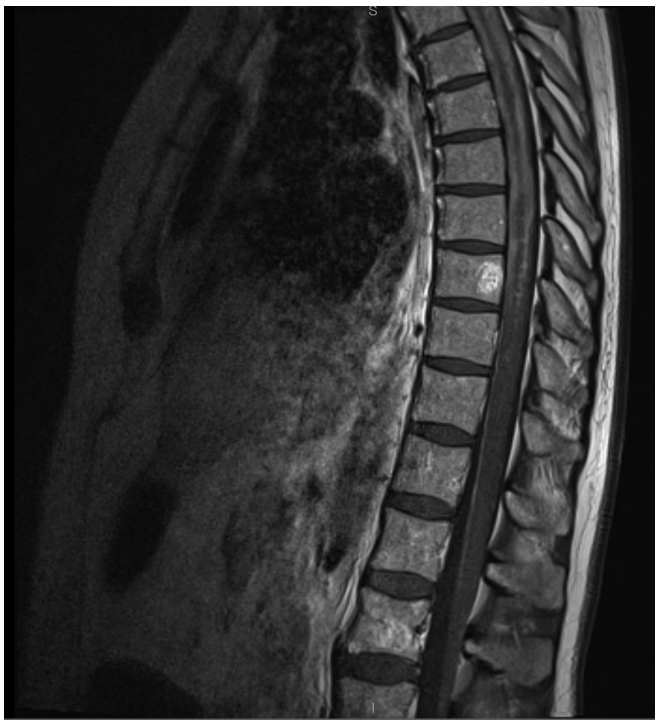

Figure 1. Thoracic spine MRI showing increased T2 signal, consistent with LETM

inhibitors. The patient was transferred to the Neurology Department (ND). On admission, severe paresis of the lower extremities, with little movement only in the digits of the left foot observed. Patellar reflexes were present symmetrically, plantar reflexes weaker in the left extremity, with Babinski reflex present bilaterally, and no superficial sensation bilaterally from Th6 downwards to the level of the upper part of the lower leg, hyperesthesia present in the parts of the lower extremities below. Antibiotic therapy and methylprednisolone treatment were continued, both at a dose of 1 g. Significant improvement in the mobility of lower extremities was observed in the following days. However, after the third infusion of methylprednisolone, rash and dyspnea occurred, so the dose was reduced to 256 mg and the administration route was changed to oral. Plasmapheresis was performed five times. A lumbar puncture was subsequently conducted, revealing a high level of protein (268 mg/dl) in the cerebrospinal fluid (CSF) and cytosis of 13. CSF was also tested for PCR test of adenoviruses, CMV, EBV, Borrelia antibodies, and oligoclonal antibodies. All of them were negative. No atypical cells were shown in flow cytometry. The diagnosis was expanded by an ophthalmologic consultation. Visual evoked responses were intact, with no signs of neuropathy or ophthtalmoneuritis found. During hospitalization, a slow but gradual improvement in neurological function was observed. Unfortunately, the patient developed diabetes, with fasting blood glucose levels of 156 mg/dl, most likely as a result of corticosteroid therapy. Metformin (1 g once daily) was administered along with a diabetic diet, which led to the normalization of glucose levels. Moreover, the patient experienced a recurrence of hemorrhoids (after many years). An ointment containing tribenoside and lidocaine hydrochloride was prescribed. NMO-SD was diagnosed based on the clinical presentation (LETM), positive test for AQP4-Ab IgG, acute myelitis, and the exclusion of alternative diagnoses. The diagnosis was made according to the consensus diagnostic criteria [12], which are presented in Table 1. The patient was transferred to the Neurological Rehabilitation Department at Wolski Hospital on November 11th, 2023, to continue methylprednisolone treatment (64 mg p.o. for the next 5 days, then reduced to 32 mg). A follow-up was planned for January 2024.

Discussion

To the best of our knowledge, we report the first case of LETM in Poland. Only cases of TM, other than LETM, have been reported previously. The case occurred in an immunocompetent host. LETM is a rare entity that can lead to severe and potentially irreversible clinical complications. LETM is often associated with a poor prognosis, especially if it occurs in conjunction with NMO [13]. Moreover, it can co-exist with other lesions in the CNS, such as spinal cord infarction, acute disseminated encephalomyelitis, and multiple sclerosis [14]. A retrospective study (n = 192) found a recurrence rate of approximately 57% [15]. Multiple risk factors for recurrence were identified, including African American race, female sex, and the development of NMOSD [16]. Transverse myelitis is an inflammatory process affecting the spinal cord, strongly associated with an immune response. The clinical course of LETM is characterized by at least one episode of paraparesis or tetraparesis [17]. Furthermore, it is often associated with sensory deficits and disturbances in bowel/bladder function. There are two types of TM based on their causative agent: idiopathic TM and secondary TM [18]. Secondary TM can have a variety of origins. Potential causative agents include HIV, coronaviruses, CMV, Borrelia, Mycoplasma, Mycobacterium, as well as autoimmune diseases such as SLE and others. All these factors must be taken into consideration when managing patients with LETM. Severe cases can lead to respiratory failure, which is the primary concern in cases with a rapid onset. This was also a major issue in our case; hence, we acted promptly to provide a rapid diagnosis and implement appropriate treatment with methylprednisolone, which remains the therapy of choice. LETM can occur with, which was the case of our patient, or without AQP-Ab. There are significant differences between these two variants of the disease, for example, patients with positive AQP4-Ab are substantially more prone to recurring episodes of central nervous system inflammation and less likely to develop initial urinary retention than patients without these antibodies [19]. In contrast, our patient developed initial urinary retention despite the presence of AQP-4Ab. Clinical diagnosis of LETM is based primarily on spinal MRI showing a lesion spanning at least three vertebral segments [20]. The diverse nature of LETM and its association with various underlying conditions and diseases highlights the importance of a thorough evaluation for an accurate diagnosis and appropriate management. In our case, conditions such as COVID-19, meningitis, SLE, syphilis, vitamin B12 deficiency, Borrelia infection, and others were discarded, leading to the conclusion that LETM in our patient was caused by bacteria responsible for the original left-sided pneumonia. This is an unusual occurrence, especially given the moderate severity of the infection and the patient's overall good condition. We conducted a thorough search through PubMed and Google Scholar for cases of bacteria-associated LETM, and only five were found, as described in Table 2. The clinical courses of these cases varied significantly from ours. Their first manifestations were diversified, with only one of them beginning with abdominal pain. In none of them, AQP4-Ab were present, and neither were anti-MOG Ab, nor post-steroidal diabetes. On the other

Table 1. Consensus diagnostic criteria for NMO-SD

1. At least 1 core clinical characteristic 2. Positive test for AQP4-IgG (cell-based assay recommended) 3. Exclusion of alternative diagnoses	Core clinical characteristics: 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome 4. Acute brainstem syndrome 5. Symptomatic narcolepsy 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Table 2. Clinical course of other bacteria-caused LETM cases

Case author	Causative bacterium	First manifestation	Urinary retention	MRI – increased T2 signal	AQP4-Ab	anti-MOG	Post-steroidal diabetes
Williams, and Thorpe [21]	*S. pneumoniae*	Increasing lower limb weakness	+	+	-	-	-
Kilic [22]	*M. pneumoniae*	Back pain, lower limb weakness, dizziness	+	+	-	-	-
Heller et al. [23]	*S. pneumoniae*	Bilateral hip-pain	+	-	-	-	-
Csabi et al. [24]	*M. pneumoniae*	Severe abdominal pain	+	+	-	-	-
He et al. [25]	*M. pneumoniae*	Lower extremity weakness, paresthesia, decreased sensation	+	+	-	-	-

hand, urinary retention was observed in four out of five cases, and so was increased T2-signal on MRI. Furthermore, our patient presented with persistent hiccups and vomiting, which are very rare findings in LETM patients – both post-viral and post-bacterial. Most of the cases identified in the literature were caused by SARS-CoV-2. Our patient was COVID-19 negative and responded positively to ceftriaxone treatment. Therefore, we suspect cross-reactivity between the bacteria which caused the unilateral pneumonia and AQP-4. However, one study involving 114 patients found no evidence for this molecular link with Klebsiella pneumoniae [26]. Hence, we hypothesize that different bacteria were the causative agent. We reviewed SARS-CoV-2 provoked cases of LETM in order to compare the level of protein in CSF with our patient, for whom it was 268 mg/dl. We included 25 cases into our analysis and the results were as follows: range 39–281 mg/dl, average 100.5 mg/dl ± 25.5. In comparison, our patient presented a relatively high level of protein, which might be a potential differentiating factor between viral and bacterial LETM. The patient's response to treatment, including intravenous methylprednisolone, plasmapheresis, and antibiotic therapy, along with the gradual improvement in neurological function during hospitalization, demonstrates the importance of early intervention and a multidisciplinary approach to managing cases of LETM. However, caution is needed when administering steroids for LETM treatment, given the risk of developing diabetes. Our patient, unfortunately, developed post-steroidal diabetes in the course of treatment and required metformin. While this additional medication can impact the patient's quality of life, it was necessary to prevent more serious complications. It is also important to be aware of possible hemorrhoids occurrence; therefore, physiotherapy and rehabilitation ought to be implemented as early as possible.

Conclusions

The reported case is highly unusual, given the fact that it occurred following bacterial pneumonia and presented with persistent hiccups and vomiting. The novelty of this case also lies in its atypical onset with initial presentation as girdle pain in the abdomen. Magnetic resonance imaging is the primary method of diagnosis and can help exclude other possible etiologies of neurological symptoms. When managing LETM, timing is critical to prevent paralysis of the respiratory muscles. LETM remains an extremely rare condition and with diverse origins as well as clinical manifestations, and its management continues to present a significant challenge.

Authors declare no conflict of interest, no competing interest.

Authors declare no external funding.

Authors would like Dr Mikołaj Radziszewski for providing us with information about the case.

References

1. Trebst C, Raab P, Voss EV, et al. Longitudinal extensive transverse myelitis – it's not all neuromyelitis optica. Nat Rev Neurol, 2011; 7: 688–698. doi: 10.1038/nrneurol.2011.176
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology, 2015; 85: 177–189. doi: 10.1212/WNL.0000000000001729
3. Li R, Zhong X, Qiu W, et al. Association between neuromyelitis optica and tuberculosis in a Chinese population. BMC Neurol, 2014; 14: 33. doi: 10.1186/1471-2377-14-33
4. Topcu Y, Bayram E, Karaoglu P, et al. Coexistence of myositis, transverse myelitis, and Guillain Barré syndrome following *Mycoplasma pneumoniae* infection in an adolescent. J Pediatr Neurosci, 2013; 8: 59–63. doi: 10.4103/1817-1745.111428
5. Nath A. Neurologic manifestations of severe acute respiratory syndrome coronavirus 2 infection. Continuum (Minneap Minn), 2021; 27: 1051–1065. doi: 10.1212/CON.0000000000000992
6. Baig AM, Sanders EC. Potential neuroinvasive pathways of SARS-CoV-2: deciphering the spectrum of neurological deficit seen in coronavirus disease-2019 (COVID-19). J Med Virol, 2020; 92: 1845–1857. doi: 10.1002/jmv.26105
7. Munz M, Wessendorf S, Koretsis G, et al. Acute transverse myelitis after COVID-19 pneumonia. J Neurol, 2020; 267: 2196–2197. doi: 10.1007/s00415-020-09934-w
8. Shahali H, Ghasemi A, Farahani RH, et al. Acute transverse myelitis after SARS-CoV-2 infection: a rare complicated case of rapid onset paraplegia. J Neurovirol, 2021; 27: 354–358. doi: 10.1007/s13365-021-00957-1
9. Maroufi SF, Naderi Behdani F, et al. Longitudinally extensive transverse myelitis after Covid-19 vaccination: case report and review of literature. Hum Vaccin Immunother, 2022; 18: 2040239. doi: 10.1080/21645515.2022.2040239
10. Verkman AS, Phuan PW, Asavapanumas N, Tradtrantip L. Biology of AQP4 and anti-AQP4 antibody: therapeutic implications for NMO. Brain Pathol, 2013; 23: 684–695. doi: 10.1111/bpa.12085

11. Jarius S, Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. Brain Pathol, 2013; 23: 661–683. doi: 10.1111/bpa.12084
12. Wingerchuk DM, Banwell B, Bennett JL, et al.; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology, 2015; 85: 177–189. doi: 10.1212/WNL.0000000000001729
13. Sahoo LK, Mallick AK, Mohanty G, et al. Study of Clinicoradiological Profile and Prognosis of Longitudinally Extensive Transverse Myelitis from a Single Tertiary Center in Eastern India. Neurol India, 2020; 68: 1079–1083. doi: 10.4103/0028-3886.294544
14. Synmon B, Phukan P, Sharma SR, Hussain M. Etiological and Radiological Spectrum of Longitudinal Myelitis: A Hospital-Based Study in North East India. J Neurosci Rural Pract, 2021; 12: 739–744. doi: 10.1055/s-0041-1735826
15. Kimbrough DJ, Mealy MA, Simpson A, Levy M. Predictors of recurrence following an initial episode of transverse myelitis. Neurol Neuroimmunol Neuroinflamm, 2014; 1: e4. doi: 10.1212/NXI.0000000000000004
16. Maillart E, Durand-Dubief F, Louapre C, et al.; OFSEP, SFSEP, and NOMADMUS study groups. Outcome and risk of recurrence in a large cohort of idiopathic longitudinally extensive transverse myelitis without AQP4/MOG antibodies. J Neuroinflammation, 2020; 17: 128. doi: 10.1186/s12974-020-01773-w
17. Nightingale H, Witherick J, Wilkins A. Diagnosis of longitudinally extensive transverse myelitis. BMJ Case Rep, 2011; 2011: bcr1020103444. doi: 10.1136/bcr.10.2010.3444
18. Montalvo R, Sánchez Vidal M-F. Longitudinally Extensive Transverse Myelitis Associated with Cytomegalovirus Infection in an Immunocompetent Patient. *Microbiol Res*, 2022; *13*: 523–529. doi: 10.3390/microbiolres13030036
19. Kitley J, Leite MI, Küker W, et al. Longitudinally extensive transverse myelitis with and without aquaporin 4 antibodies. *JAMA Neurol*, 2013; 70: 1375–1381. doi: 10.1001/jamaneurol.2013.3890
20. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. Lancet Neurol, 2007; 6: 805–15. doi: 10.1016/S1474-4422(07)70216-8
21. Williams T, Thorpe J. Post-infective transverse myelitis following *Streptococcus pneumoniae* meningitis with radiological features of acute disseminated encephalomyelitis: a case report. J Med Case Rep, 2012; 6: 313. doi: 10.1186/1752-1947-6-313.
22. Kılıç B. Acute Transverse Myelitis Related to Mycoplasma pneumonia. J Pediatr Neurol, 2019; 18: 169–170. doi: 10.1055/s-0039-1698427
23. Heller L, Keren O, Mendelson L, Davidoff G. Transverse myelitis associated with mycoplasma pneumoniae: case report. Paraplegia, 1990; 28: 522–525. doi: 10.1038/sc.1990.69
24. Csábi G, Komáromy H, Hollódy K. Transverse myelitis as a rare, serious complication of *Mycoplasma pneumoniae* infection. Pediatr Neurol, 2009; 41: 312–313. doi: 10.1016/j.pediatrneurol.2009.04.029
25. He CB, Lee JR, Kahana M. *Mycoplasma pneumoniae* Associated Acute Transverse Myelitis: An Atypical Clinical Presentation in an Adolescent Child. Cureus, 2021; 13: e17259. doi: 10.7759/cureus.17259. Erratum in: Cureus. 2021; 13: c51. doi: 10.7759/cureus.c51
26. Jarius S, Wandinger KP, Platzer S, Wildemann B. Homology between *Klebsiella pneumoniae* and human aquaporin-4: no evidence for cross-reactivity in neuromyelitis optica. A study on 114 patients. J Neurol, 2011; 258: 929–931. doi: 10.1007/s00415-010-5839-2