Review

New pathogens causing CNS infections

Udaya K. Ranawaka[1]

Sri Lanka Journal of Neurology, 2019, **6**, 2-6

Abstract

Many emerging infections, mainly viruses, are contributing to the reshaping of the global landscape of central nervous system (CNS) infections. Several new organisms causing CNS infection have been discovered over the last decade, and new neurological syndromes have been described for many other known pathogens. Advances in diagnostic techniques such as modern DNA amplification methods have led to the detection of some of the newly identified pathogens. The global attention generated by disease epidemics has helped in the improved understanding of the neurological complications associated with some known pathogens, such as Zika virus, Ebola virus and Enterovirus D68. A better understanding of the evolution of the new pathogens, their host-vector-environment dynamics, and their disease causation is clearly needed for us to be better prepared to meet these emerging threats.

Central nervous system (CNS) infections produce large numbers of death and disability, especially in resource-limited settings such as Sri Lanka[1,2]. Early targeted treatment is crucial in minimising the deaths and disability[1,3,4]. Early targeted treatment, however, depends on establishing a microbiological diagnosis early, and this appears to be easier said than done. Globally, an aetiology is not detected in 85% of cases suspected CNS infection[5]. Lack of diagnostic facilities in resource-limited settings is an important reason for the low diagnostic yields[1,6], but a definitive cause is not found in over 60% of cases even in studies conducted with good microbiological support in settings without resource limitations[5,7,8]. Studies on the epidemiology of CNS infection in Sri Lanka are limited, but the available data show similar low isolation rates ranging from 0.5% to 27.3%[9,10,11,12,13,14,15].

The global landscape of CNS infections, it seems, is changing. Many factors contribute to this, but a key reason is the emergence and re-emergence of many neurotropic pathogens[15,16]. This review will focus on CNS infections caused by several new organisms described in the last decade. Some of them are newly discovered organisms, whereas some are well known pathogens previously not associated with CNS involvement.

New kids on the block: novel pathogens producing CNS disease

Encephalitis from squirrels: Variegated squirrel Bornavirus

Between 2011 and 2013, three men from the same geographical area (Saxony-Anhalt) in Germany developed an unexplained progressive fatal meningo-encephalitis. Clinical features included confusion, ataxia, myoclonus, ocular paresis, psychomotor slowing and coma, and they died 2-4 months after onset of the illness. MRI changes were seen in cortical areas, basal ganglia and brainstem with meningeal enhancement; spinal cord was not affected. They were breeders of variegated squirrels *(Sciurus variegatoides)* and members of the same squirrel-breeding club, and had exchanged their pet squirrels on many occasions. Two of them had reported bites and scratch injuries by the squirrels[17]. On meta-genomic studies, a new bornavirus (named Variegated squirrel Bornavirus-1; VSBV-1) was detected in CNS samples from the three patients, with detection of viral RNA from brain biopsy tissue and anti-Bornavirus IgG antibodies in blood and CSF. Nearly identical generic sequences were detected from one squirrel[17,18].

Borna viruses are single-stranded RNA viruses. Borna disease (1st described in 1885 among cavalry horses in the town of Borna, Germany) is a well known encephalitic illness in horses and sheep, and is caused by the Borna disease viruses (BoDV). VSBV-1 is considered to be a different virus belonging to the same genus and family[17,19]. There is some debate over the causation of human disease by BoDV-1[17,19]. Interestingly, four cases of human encephalitis due to BoDV-1, with 3 of them transmitted by solid organ transplantation from a single donor, were reported in March 2018, again from Germany[19].

Bocavirus and Encephalitis

Human Bocavirus (HBoV) is a single stranded DNA virus of the Parvovirus family, first described in Sweden in 2005. It has been associated with acute respiratory infections (mainly in children) and gastroenteritis, and has been isolated from respiratory samples (genotype HBoV-1) and stools samples (mainly genotypes HBoV-1,2 and 3) worldwide[20]. More recently, the association of HBoV infection with encephalitis has been reported from several countries. The first report was in 2012, when HBoV-1 and 2 were isolated from Bangladeshi children

[1]*Professor in Neurology, Faculty of Medicine, University of Kelaniya, Sri Lanka.*
Correspondence: Udaya K. Ranawaka E-mail: udayaran@yahoo.com; udayaran@kln.ac.lk

with encephalitis[21]. The second report was from Sri Lanka in 2013, where HBoV-1, 2 and 3 were detected in 5 out of 191 CSF samples from adults and children with CNS infection[11,15]. HBoV-associated encephalitis has subsequently been reported in several case series[22,23].

There is ongoing debate on whether HBoV is a true pathogen or an innocent bystander[20,24]. Diagnosis of HBoV infection is mainly based on genome detection by PCR techniques in biological samples. Culture techniques or animal models for virus isolation are still not available; as such, the true pathogenicity of HBoV remains to be defined. However, the presence of high viral loads and the decline in viral concentrations with symptom resolution are considered to be strongly suggestive of a causal role in pathogenesis[20].

CRESS-DNA viruses and CNS

CRESS-DNA viruses are a group of viruses with circular, replication initiator protein (Rep) encoding, single stranded DNA (CRESS-DNA) genomes. They are the smallest viruses known to infect mammals and carry the smallest genomes among autonomously replicating eukaryotic viruses, containing only the Rep and capsid proteins[12]. Several novel CRESS-DNA viruses have been recently reported to be associated with CNS disease.

A study from Vietnam in 2013 reported the detection of a cyclovirus in two patients with CNS infection of unknown etiology, following a search for novel pathogens causing CNS infection using next generation sequencing; the new virus was named Cyclovirus-Vietnam (CyCV-VN). It was subsequently detected in 4% of 642 CSF specimens from patients with suspected CNS infection. It was also isolated in stools from healthy children suggesting the possibility of food-borne or orofaecal transmission, and in stools from pigs and poultry suggesting the existence of animal reservoirs[25]. In 2015, the identification of two novel CRESS-DNA viruses in Sri Lankan patients with unexplained encephalitis was reported. The genomes of a cyclovirus, named Cyclovirus-Sri Lanka (CyCV-SL), and a gemycircularvirus, named Gemycircularvirus-Sri Lanka (GemyCV-SL), were detected by deep sequencing in one and three out of 201 CSF samples, respectively[12]. This was the first report of an association of encephalitis with a gemycircularvirus, and the second with a cyclovirus (following the report from Vietnam). Another report of gemycircularvirus-associated encephalitis was subsequently reported from China[26]. Another novel cyclovirus has been detected from patients with paraplegia in Malawi[27].

Similar to Bocavirus, the causal importance of these CRESS-DNA viruses in CNS infection is yet to be determined. However, it is pertinent to note that circoviruses, belonging to another genus of CRESS-DNA viruses, have been identified in serum and brain tissue of foxes and pigs with unexplained meningo-encephalitis[28,29].

Old dogs with new tricks: newly described CNS involvement with known pathogens

Zika and the CNS

Zika virus (ZIKV) is an arthropod-borne flavivirus transmitted by *Aedes aegypti* mosquitoes. It was first identified in 1947 in a Rhesus monkey in the Zika forest in Uganda, and the first human infection was reported in Nigeria in 1954[18,30,31]. It gained global attention with its recent pandemic re-emergence, with explosive outbreaks in the Pacific region (2013-14) and the Americas (2015)[18,32]. Interestingly, it followed in the wake of a pandemic of Chikungunya infection, a pattern that had been noted in Africa for decades[32]. Neurological involvement with ZIKV was first noted during these outbreaks; until then ZIKV infection was considered a self-limiting mild or subclinical viral illness[32].

A number of neurological syndromes including Guillain-Barre syndrome (GBS), encephalitis, encephalopathy, myelitis, acute disseminated encephalomyelitis, cerebral vasculopathy leading to strokes, CIDP and sensory neuropathy have been reported with ZIKV infection[30,31,32,33,34,35,36,37]. Of these, GBS appears to be the commonest manifestation[37]. The association with GBS was first described following the French Polynesian outbreak; these cases were of the acute motor axonal neuropathy (AMAN) type, but did not have the typical anti-ganglioside antibody profile of AMAN. In contrast, the majority of GBS cases in a Brazilian study were of demyelinating type[37]. ZIKV-related GBS is characterized by a short latency period following infection and rapid progression[30,31]. The association with recent ZIKV infection was demonstrated by anti-ZiV IgM serology in affected patients[30]. ZIKV associated encephalitis presents as a typical viral encephalitis. MRI changes are seen in subcortical areas, and CSF has a meningitic picture with a polymorphonuclear leucocyte-predominant pleocytosis. Presence of ZIKV in CSF has been demonstrated by RT-PCR and positive culture[33]. Unlike with other flaviviruses encephalitis and other forms of neurological involvement seems to be uncommon with ZIKV[18].

The first evidence of neurotropism of ZIKV was seen in the form of cases of microcephaly and other foetal malformations reported during the 2014-16 outbreaks [38,39,40]. An epidemic of microcephaly was noted in Brazil, with a 20-fold increase in numbers in 2014-15[32]. Women who had ZIKV infection during the first two trimesters of pregnancy were 17 times more likely to deliver a baby with microcephaly[31,40]. The association with ZIKV has been demonstrated by the presence of ZIKV genomes by RT-PCR and IgM antibodies in the CSF and serum of newborns[39]. Further, ZIKV-RNA has been detected in amniotic fluid and placentae of pregnant mothers, and foetal brain tissue of dead infants[36]. Microcephaly is

only one part of what is now recognized as 'congenital Zika syndrome'; other manifestations include cerebral atrophy, intracranial calcifications, neural tube defects, optic nerve abnormalities and hearing loss[31]. It is noteworthy that microcephaly is well documented in association with other viral infections such as rubella and CMV during pregnancy, and it has recently been reported with intrauterine infection with West Nile and Chikungunya viruses[38].

Ebola virus disease

Ebola virus is a single stranded RNA virus of the filovirus family. It was first discovered during two simultaneous outbreaks of Ebola virus disease (EVD) in 1976, in South Sudan and in a village near the Ebola river in the Democratic Republic of Congo[41]. EVD is considered to be a zoonosis, and Old World fruit bats of the Pteropodidae family are believed to be the natural hosts for the virus[41,42]. The virus is transmitted to people by handling of dead or sick forest animals (such as monkeys, chimpanzees, gorillas, antelopes or porcupines), or by contact with infected bats. Human-to-human transmission occurs through blood or body fluids, including sexual transmission[41,42]. To date, EVD outbreaks have been confined to the African continent, but the possibility of transcontinental spread due to global air travel remains a major concern[42].

EVD is a viral haemorrhagic fever with 50-80% case fatality[41,42]. Neurological involvement is considered uncommon[42], but has been reported in up to one-third of patients in some series. Some neurological manifestations (seizures, confusion, meningism, tinnitus and hearing loss) were reported during a 1995 Ebola outbreak in the Democratic Republic of the Congo, however, these were not well documented or investigated[43]. Neurological complications first came into prominence during the largest ever outbreak of Ebola virus infection in West Africa (Guinea, Sierra Leone, Liberia) in 2014-16[18]. The main neurological findings included seizures, encephalopathy, encephalitis, meningitis and frontal lobe dysfunction[18, 44, 45, 46]. Cortical atrophy, subcortical white matter lesions and spinal cord lesions have been reported on MRI[44,45]. Detection of Ebola virus genomes in CSF and serum by RT-PCR is the mainstay of diagnosis[45,46,47]. Serological tests are of limited value as they may be negative in fatal cases[42]. Residual cognitive deficits and neurological sequelae have been reported in many patients[18,45]. The virus is thought to be capable of persisting in immunologically privileged sanctuary sites such as the CNS, and producing late relapsing infection and delayed transmission[18,45]. Several cases of late encephalitis and meningitis among survivors have been reported[45,48].

Enteroviruses and the CNS

Beginning 2012, a large number of cases of acute flaccid paralysis of unexplained aetiology were reported from various regions in the United States. The illness was characterised by rapid onset paralysis and cranial neuropathy, and was termed Acute Flaccid Myelitis (AFM). The weakness was asymmetric, proximal more than distal, and with upper extremity more than lower extremity involvement. CSF showed pleocytosis with elevated proteins, and involvement of spinal cord grey matter and brain stem was seen on MRI. Epidemiological studies revealed a strong association with Enterovirus D68 (EV-D68), which is usually a respiratory pathogen, and the virus was identified in respiratory secretions of affected children[49,50,51]. Long term residual neurological deficits have been reported in many of the children[52].

Enterovirus A71 (EV-A 71) is better known to produce CNS involvement. It usually causes hand, foot and mouth disease (HFMD) in children, and has recently caused large outbreaks in Southeast Asia and the Pacific region[53]. It was first isolated in 1969 from a child with encephalitis in California, USA[54], but gained global attention due to the high rate of neurological complications and case fatality during the more recent outbreaks[53,54]. EV-A71 produces an aseptic meningitis, similar to other enteroviuses. However, unlike them, it is capable of invading the brainstem, cerebellum and spinal cord. Brainstem involvement with damage to the vasomotor and respiratory centres in the medulla is believed to be responsible for the severe pulmonary oedema seen in some patients[55]. The spectrum of neurological disorders includes meningitis, encephalitis, paralytic syndrome, myoclonus, tremors, ataxia, Guillain Barre syndrome and transverse myelitis, with or without the presence of HFMD [53,54,55].

CONCLUSION

Many CNS infections remain undiagnosed, and it is likely that many of these are caused by newly emerging infections. Several such emerging infections have been characterised in the last decade, contributing to the changing landscape of CNS infection. Outbreak investigations have helped define the neurological syndromes associated with some known pathogens (such as Zika, Ebola, EV-A71), whereas searching for elusive pathogens with modern diagnostic methods has enabled the discovery of several novel organisms producing CNS infection (e.g., VSBV-1). The pathogenic role of some of the newer pathogens is yet to be confirmed. No specific treatments or vaccines are currently available for many of these infections, and disease surveillance and prevention are the cornerstones of minimising deaths and disability caused by them. The disease patterns are hauntingly similar to some epidemics from yesteryear (e.g, EV-A 71 and polio), and learning from the past lessons would stand us in good stead in facing the new threats.

Key points

- The global landscape of central nervous system infections is rapidly changing.
- Neurological syndromes caused by many emerging organisms, mainly viruses, have been defined in the last decade.
- Epidemic surveillance and investigation have helped in the characterisation of many such neurological syndromes.
- Advances in diagnostic techniques have led to the discovery of many new pathogens causing central nervous system infections.

References

1. Scarborough M, Thwaites GE. The diagnosis and management of acute bacterial meningitis in resource-poor settings. *Lancet Neurol.* 2008; **7**: 637-48.
2. Anon. Battling bacterial meningitis in developing countries. *Lancet Neurol.* 2008; **7**: 561.
3. Køster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. *J Infect.* 2008; **57**: 449-54.
4. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM* 2005; **98**: 291-98.
5. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; **10**: 835-44.
6. Scarborough M, Gordon SB, Whitty CJ, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007; **357**: 2441-50.
7. Michael BD, Sidhu M, Stoeter D, Roberts M, Beeching NJ, Bonington A, et al. North West Neurological Infections Network. Acute central nervous system infections in adults--a retrospective cohort study in the NHS North West region. *QJM.* 2010; **103**: 749-58.
8. Glaser CA, Gilliam S, Schnurr D, Forghani B, Honarmand S, Khetsuriani N, et al. California Encephalitis Project, 1998-2000. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clin Infect Dis* 2003; **36**: 731-42.
9. Batuwanthudawe R, Karunarathne K, Dassanayake M, de Silva S, Lalitha MK, Thomas K, et al. Surveillance of invasive pneumococcal disease in Colombo, Sri Lanka. *Clin Infect Dis* 2009; **48** Suppl 2: S136-40.
10. Ranawaka UK, Rajindrajith EG, Perera KV, Dassanayake KM, Premaratne BA, de Silva HJ. Clinical profile and difficulties in diagnosis of central nervous system infections in adult patients in a tertiary care hospital. *Ceylon Med J* 2013; **58**: 26-8.
11. Mori D, Ranawaka U, Yamada K, Rajindrajith S, Miya K, Perera HK, et al. Human bocavirus in patients with encephalitis, Sri Lanka, 2009-2010. *Emerg Infect Dis.* 2013; **19**: 1859-62.
12. Phan TG, Mori D, Deng X, Rajindrajith S, Ranawaka U, Fan Ng TF, et al. Small circular single stranded DNA viral genomes in unexplained cases of human encephalitis, diarrhea, and in untreated sewage. *Virology* 2015; **482**: 98-104.
13. Lohitharajah J, Malavige N, Arambepola C, Wanigasinghe J, Gamage R, Gunaratne P, et al. Viral aetiologies of acute encephalitis in a hospital-based South Asian population. *BMC Infect Dis* 2017; **17**: 303.
14. Danthanarayana N, Williams DT, Williams SH, Thevanesam V, Speers DJ, Fernando MS. Acute meningoencephalitis associated with echovirus 9 infection in Sri Lanka, 2009. *J Med Virol* 2015; **87**: 2033-9.
15. Udaya K. Ranawaka. PB Fernando Oration 2017. The challenge of treating central nervous system infections in the developing world. *Journal of the Ceylon College of Physicians* 2019 (in press).
16. Ranawaka UK. The challenge of treating central nervous system infections. *Ceylon Med J* 2015; **60**: 155-8.
17. Hoffmann B, Tappe D, Höper D, Herden C, Boldt A, Mawrin C, et al. A Variegated Squirrel Bornavirus Associated with Fatal Human Encephalitis. *N Engl J Med.* 2015; **373**: 154-62.
18. Mailles A, Stahl JP, Bloch KC. Update and new insights in encephalitis. *Clin Microbiol Infect* 2017; **23**: 607-13.
19. European Centre for Disease Prevention and Control. Acute encephalitis associated with infection with Borna disease virus 1 - Germany, 2018. 26 March 2018. Stockholm: ECDC; 2018. https://ecdc.europa.eu/sites/portal/files/documents/09-03-2018-RRA-Borna%20disease%20virus-Germany.pdf (Accessed 16 June 2019).
20. Guido M, Tumolo MR, Verri T, Romano A, Serio F, De Giorgi M, et al. Human bocavirus: Current knowledge and future challenges. *World J Gastroenterol.* 2016; **22**: 8684-97.
21. Mitui MT, Tabib SM, Matsumoto T, Khanam W, Ahmed S, Mori D, et al. Detection of human bocavirus in the cerebrospinal fluid of children with encephalitis. *Clin Infect Dis* 2012; **54**: 964-7.
22. Yu JM, Chen QQ, Hao YX, Yu T, Zeng SZ, Wu XB, Zhang B, Duan ZJ. Identification of human bocaviruses in the cerebrospinal fluid of children hospitalized with encephalitis in China. *J Clin Virol* 2013; **57**: 374-7.
23. Ergul AB, Altug U, Aydin K, Guven AS, Altuner Torun Y. Acute necrotizing encephalopathy causing human bocavirus. *Neuroradiol J.* 2017; **30**: 164-7.
24. Deresinski S. Encephalitis and Bocavirus? *Clin Infect Dis* 2014; **58**: iii-iv.
25. Tan le V, van Doorn HR, Nghia HD, Chau TT, Tu le TP, de Vries M, et al. Identification of a new cyclovirus in cerebrospinal fluid of patients with acute central nervous system infections. *MBio* 2013; **4**: e00231-13.
26. Zhou C, Zhang S, Gong Q, Hao A. A novel gemycircularvirus in an unexplained case of child encephalitis. *Virol J* 2015; **12**: 197.
27. Smits SL, Zijlstra EE, van Hellemond JJ, Schapendonk CM, Bodewes R, Schürch AC, et al. Novel cyclovirus in human

cerebrospinal fluid, Malawi, 2010-2011. *Emerg Infect Dis* 2013; **19**(9): 1511-13.

28. Bexton S, Wiersma LC, Getu S, van Run PR, Verjans GM, Schipper D, et al. Detection of Circovirus in Foxes with Meningoencephalitis, United Kingdom, 2009-2013. *Emerg Infect Dis* 2015; **21**: 1205-8.
29. Bukovsky C, Schmoll F, Revilla-Fernández S, Weissenböck H. Studies on the aetiology of non-suppurative encephalitis in pigs. *Vet Rec* 2007; **161**: 552-8.
30. Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet* 2016; **387**: 1531-9.
31. Tyler KL, Roos KL. The Expanding Spectrum of Zika Virus Infections of the Nervous System. *JAMA Neurol* 2017; **74**: 1169-71.
32. Fauci AS, Morens DM. Zika Virus in the Americas – Yet Another Arbovirus Threat. *N Engl J Med* 2016; **374**: 601-4.
33. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S, et al. Zika Virus Associated with Meningoencephalitis. *N Engl J Med* 2016; **374**: 1595-6.
34. Niemeyer B, Niemeyer R, Borges R, Marchiori E. Acute Disseminated Encephalomyelitis Following Zika Virus Infection. *Eur Neurol* 2017; **77**: 45-6.
35. Mécharles S, Herrmann C, Poullain P, Tran TH, Deschamps N, Mathon G, et al. Acute myelitis due to Zika virus infection. *Lancet* 2016; **387**: 1481.
36. Carod-Artal FJ. Neurological complications of Zika virus infection. *Expert Rev Anti Infect Ther* 2018; **16**: 399-410.
37. da Silva IRF, Frontera JA, Bispo de Filippis AM, Nascimento OJMD; RIO-GBS-ZIKV Research Group. Neurologic Complications Associated With the Zika Virus in Brazilian Adults. *JAMA Neurol* 2017; **74**: 1190-98.
38. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. *Lancet* 2016; **387**: 2125-32.
39. de Araújo TVB, Ximenes RAA, Miranda-Filho DB, Souza WV, Montarroyos UR, de Melo APL, et al. Investigators from the Microcephaly Epidemic Research Group; Brazilian Ministry of Health; Pan American Health Organization; Instituto de Medicina Integral Professor Fernando Figueira; State Health Department of Pernambuco. Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study. *Lancet Infect Dis* 2018; **18**: 328-36.
40. Brady OJ, Osgood-Zimmerman A, Kassebaum NJ, Ray SE, de Araújo VEM, da Nóbrega AA, et al. The association between Zika virus infection and microcephaly in Brazil 2015-2017: An observational analysis of over 4 million births. *PLoS Med* 2019; **16**: e1002755.
41. World Health Organization. Ebola virus disease. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease. (Accessed 15 June 2019).
42. Malvy D, McElroy AK, de Clerck H, Günther S, van Griensven J. Ebola virus disease. *Lancet* 2019; **393**: 936-48.
43. Bwaka MA, Bonnet MJ, Calain P, Colebunders R, De Roo A, Guimard Y, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. *J Infect Dis* 1999; **179** Suppl 1: S1-7.
44. Chertow DS, Nath A, Suffredini AF, Danner RL, Reich DS, Bishop RJ, et al. Severe Meningoencephalitis in a Case of Ebola Virus Disease: A Case Report. *Ann Intern Med* 2016; **165**(4): 301-4.
45. Howlett P, Brown C, Helderman T, Brooks T, Lisk D, Deen G, et al. Ebola Virus Disease Complicated by Late-Onset Encephalitis and Polyarthritis, Sierra Leone. *Emerg Infect Dis* 2016; **22**(1): 150-2.
46. de Greslan T, Billhot M, Rousseau C, Mac Nab C, Karkowski L, Cournac JM, et al. Ebola Virus-Related Encephalitis. *Clin Infect Dis* 2016; **63**(8): 1076-8.
47. Sagui E, Janvier F, Baize S, Foissaud V, Koulibaly F, Savini H, et al. Severe Ebola Virus Infection With Encephalopathy: Evidence for Direct Virus Involvement. *Clin Infect Dis* 2015; **61**(10): 1627-8.
48. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet* 2016; **388**: 498-503.
49. Messacar K, Schreiner TL, Maloney JA, Wallace A, Ludke J, Oberste MS, et al. A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA. *Lancet* 2015; **385**: 1662-71.
50. Messacar K, Schreiner TL, Van Haren K, Yang M, Glaser CA, Tyler KL, Dominguez SR. Acute flaccid myelitis: A clinical review of US cases 2012-2015. *Ann Neurol* 2016; **80**: 326-38.
51. Wiznitzer M, Nath A. Acute flaccid myelitis and enterovirus D68: Déjà vu all over again. *Neurology* 2017; **89**: 112-13.
52. Martin JA, Messacar K, Yang ML, Maloney JA, Lindwall J, Carry T, et al. Outcomes of Colorado children with acute flaccid myelitis at 1 year. *Neurology* 2017; **89**: 129-37.
53. Tyler KL. Emerging viral infections of the central nervous system: part 1. *Arch Neurol* 2009; **66**: 939-48.
54. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002; **359**: 507-13.
55. Modlin JF. Enterovirus déjà vu. *N Engl J Med* 2007; **356**: 1204-5.