

DECADE IN REVIEW—CNS INFECTIONS

## Major advances against a moving target of CNS infections

Lisa F. P. Ng and Tom Solomon

**CNS infections have severe manifestations, often leading to high mortality, but the CNS is usually not the primary target of pathogens, leaving a window of opportunity to prevent neuroinvasion. We must prioritize development of therapies to prevent neurological sequelae that cause long-lasting morbidity and disease burden on society.**

The Nobel Prize in Physiology or Medicine in 2015 was awarded jointly for discoveries concerning novel therapies against malaria and infections caused by roundworm parasites, highlighting the global importance of infectious disease. The past decade has seen some considerable advances in the diagnosis and treatment of CNS infections, despite some major challenges, such as the emergence of novel pathogens, the spread of existing pathogens to new geographical areas as a result of travel and climate change, and more-severe outbreaks caused by existing pathogens becoming more virulent, and increasing numbers of immunocompromised people. As organizers of the Gordon Research Conferences on Infections of the Nervous System in 2013 and 2015, we have had the opportunity to closely follow the advances made in the prevention and treatment of CNS infections. Despite these advances, many unmet challenges remain, including the rise of resistance to the antimalarial drug artemisin in patients with severe cerebral malaria, which has increased morbidity and mortality, re-emergence of arbovirus-induced CNS disease, limited treatment options for cryptococcal meningitis, and failure of the Japanese encephalitis vaccine, to name a few.

In the USA and developed European countries, viral encephalitis, bacterial meningitis and Lyme neuroborreliosis have been

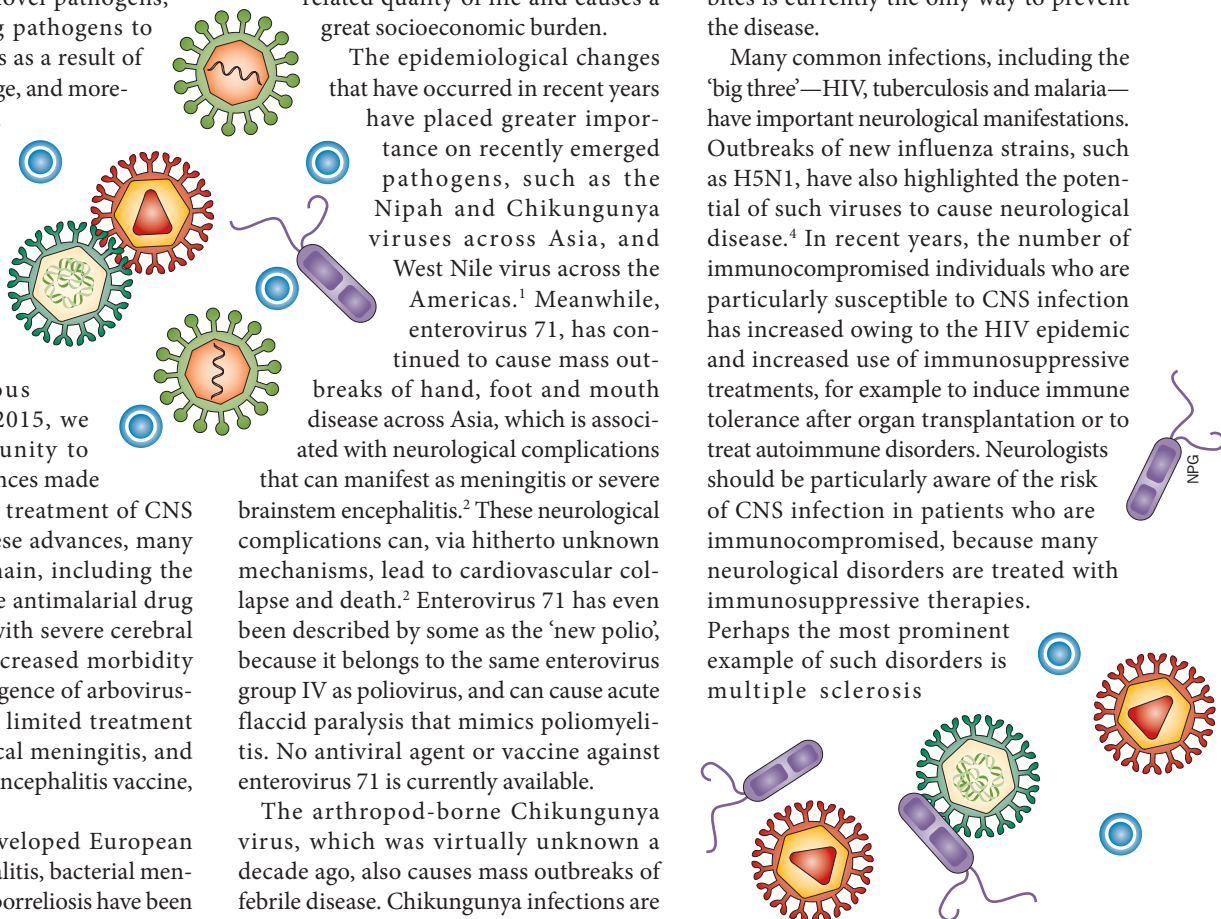
studied fervently. Less attention has been given to potentially fatal nervous system invasion by neurotropic viruses, parasites or mycobacteria; encephalitides caused by these pathogens are more common in developing than developed countries, and are an important health issue in resource-poor regions, because many of the survivors are left with disability that reduces health-related quality of life and causes a great socioeconomic burden.

The epidemiological changes that have occurred in recent years have placed greater importance on recently emerged pathogens, such as the Nipah and Chikungunya viruses across Asia, and West Nile virus across the Americas.<sup>1</sup> Meanwhile, enterovirus 71, has continued to cause mass outbreaks of hand, foot and mouth disease across Asia, which is associated with neurological complications that can manifest as meningitis or severe brainstem encephalitis.<sup>2</sup> These neurological complications can, via hitherto unknown mechanisms, lead to cardiovascular collapse and death.<sup>2</sup> Enterovirus 71 has even been described by some as the ‘new polio’, because it belongs to the same enterovirus group IV as poliovirus, and can cause acute flaccid paralysis that mimics poliomyelitis. No antiviral agent or vaccine against enterovirus 71 is currently available.

The arthropod-borne Chikungunya virus, which was virtually unknown a decade ago, also causes mass outbreaks of febrile disease. Chikungunya infections are

characterized by fever, headache, rashes, and debilitating arthralgia that can continue for years after infection. Atypical manifestations have also been described, and include neurological symptoms that range from simple and complex febrile seizures to meningeal syndrome, acute encephalopathy, diplopia, aphasia, acute disseminated encephalomyelitis, and encephalitis.<sup>3</sup> After its first reported appearance in 1952, the virus re-emerged in the Indian Ocean islands in 2005–2006, and several outbreaks of Chikungunya infection have occurred since late 2013, particularly in the Caribbean islands and the Americas, but also in several countries in Africa and Southern Europe. Increased global travel, evolution of the virus and adaptation of mosquito vectors have all been suggested as contributing factors to the spread of the virus to new geographical areas.<sup>3</sup> No vaccination or treatment for Chikungunya virus exists, and avoiding mosquito bites is currently the only way to prevent the disease.

Many common infections, including the ‘big three’—HIV, tuberculosis and malaria—have important neurological manifestations. Outbreaks of new influenza strains, such as H5N1, have also highlighted the potential of such viruses to cause neurological disease.<sup>4</sup> In recent years, the number of immunocompromised individuals who are particularly susceptible to CNS infection has increased owing to the HIV epidemic and increased use of immunosuppressive treatments, for example to induce immune tolerance after organ transplantation or to treat autoimmune disorders. Neurologists should be particularly aware of the risk of CNS infection in patients who are immunocompromised, because many neurological disorders are treated with immunosuppressive therapies. Perhaps the most prominent example of such disorders is multiple sclerosis



(MS), for which several new drugs have been approved in the past decade. Similarly, progressive multifocal leukoencephalopathy caused by JC virus was once rare, but its prevalence has increased with that of HIV, and in the past 10 years, the use of new immunosuppressive monoclonal antibodies, such as natalizumab for MS, has become another important trigger for the disease.<sup>5</sup>

## “The ‘Holy Grail’ against CNS infections—effective neuroprotective treatment—remains elusive”

During the same period, immune-mediated encephalitis, such as anti-N-methyl-D-aspartate receptor encephalitis, has been established as a cause of encephalitis that is as important as are infections.<sup>6</sup> Occasionally, some infections of the nervous system, such as herpes simplex virus, can also trigger autoimmune encephalitis.

Improved technologies and diagnostics, such as multiplex PCR, MALDI-TOF (matrix-assisted laser desorption/ionization—time-of-flight) mass spectrometry, better immunoassays and metagenomic next-generation sequencing, have improved the speed and accuracy of discovering pathogens and identifying immune system correlates of protection from infectious disease. Despite these advances, the proportion of patients with CNS infections who are misdiagnosed remains stubbornly high.<sup>6</sup>

Treatment of some brain infections, including acute bacterial meningitis and tuberculous meningitis, has improved over the past decade owing to a better understanding of the clinical features and the ways in which they contribute to poor outcomes.<sup>7</sup> Moreover, the mechanism of corticosteroids in the treatment of some of these conditions has been better defined: the benefit of dexamethasone has been

demonstrated in adults with acute bacterial meningitis in most developed countries, as has its ability to reduce the incidence and severity of hearing loss in pneumococcal disease. However, the drug is often of no benefit to adults or children in developing, tropical countries, perhaps because patients in these countries are more likely to have untreated HIV.<sup>8</sup> In Vietnamese adults with tuberculous meningitis, dexamethasone reduced mortality and is now used for most patients with this condition.

In the past 10 years, no major advances have been made in the treatment of encephalitis beyond the use of corticosteroids. In mouse studies, monoclonal antibodies have shown promise for the treatment of some viral encephalitides, such as those caused by West Nile virus, Chikungunya virus and Japanese encephalitis virus.<sup>9</sup> RNA interference has been proposed as another treatment strategy, but the only encephalitides in which it has been studied to date are Japanese encephalitis, tick-borne encephalitis and encephalitis caused by alphaviruses, so it is a long way from clinical applications.

The ‘Holy Grail’ against CNS infections—effective neuroprotective treatment—remains elusive. Therapeutic hypothermia, which has proved useful in hypoxic brain injury after cardiac arrest, was found to be of no benefit in bacterial meningitis. Novel cocktails of antivirals and potentially neuroprotective drugs initially looked promising, but have, in most cases, failed to work.

Vaccination programmes have brought some of the biggest successes in the prevention of CNS infections. Advances include the development of new vaccines for pneumococcal meningitis and Japanese encephalitis,<sup>10</sup> and, in the case of Japanese encephalitis, improved administration methods and dosage of existing vaccines. By the time of the next Gordon Research Conference on Infections of the Nervous System in 2017, these developments should have had considerable impact.

Singapore Immunology Network, Agency for Science, Technology and Research (A\*STAR), 8A Biomedical Grove, #04-06 Immunos, Biopolis, Singapore 138648, Singapore (L.F.P.N.). Institute of Infection and Global Health, University of Liverpool, Ronald Ross Building, 8 West Derby Street, Liverpool L69 7BE, UK (T.S.).

Correspondence to: L.F.P.N.

[lisa\\_ng@immunol.a-star.edu.sg](mailto:lisa_ng@immunol.a-star.edu.sg)

doi:10.1038/nrneuro.2015.202

Published online 27 October 2015

### Competing interests

The authors declare no competing interests.

1. Jones, K. E. *et al.* Global trends in emerging infectious diseases. *Nature* **451**, 990–993 (2008).
2. Chang, L. Y. *et al.* Neurodevelopment and cognition in children after enterovirus 71 infection. *N. Engl. J. Med.* **356**, 1226–1234 (2007).
3. Weaver, S. C. & Lecuit, M. Chikungunya virus infections. *N. Engl. J. Med.* **372**, 1231–1239 (2015).
4. de Jong, M. D. *et al.* Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat. Med.* **12**, 1203–1207 (2006).
5. Kleinschmidt-DeMasters, B. K. & Tyler, K. L. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N. Engl. J. Med.* **353**, 369–374 (2005).
6. Granerod, J. *et al.* Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect. Dis.* **10**, 835–844 (2010).
7. Weisfelt, M., van de Beek, D., Spanjaard, L., Reitsma, J. B. & de Gans, J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol.* **5**, 123–129 (2006).
8. van de Beek, D. *et al.* Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurol.* **9**, 254–263 (2010).
9. Oliphant, T. *et al.* Development of a humanized monoclonal antibody with therapeutic potential against West Nile virus. *Nat. Med.* **11**, 522–530 (2005).
10. Tauber, E. *et al.* Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* **370**, 1847–1853 (2007).