paraventricular thalamus were important to maintain wakefulness, and this nucleus is now identified as a crucial brain structure in sleep-wake regulation.[11]

In summary, these 2018 studies have greatly progressed our knowledge on excessive sleepiness, cognitive health, biomarkers, and brain nuclei relevant to both sleep and wakefulness.

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Advances on neurological infections in 2018

In neurological research, the realm of infections has grown to include potential infectious causes of nervous system disorders of unknown aetiology, not only the pathogenesis of neurological infections and improvements in antimicrobial therapy, but also the use of infectious agents as vectors for gene therapy. In our view, the most important developments in this field in 2018 were related to pathogenesis and treatment.

Microbes and viruses might contribute to the onset and progression of Alzheimer's disease. A study[1] reports the construction of an integrated network of genomic, transcriptomic, proteomic, and histopathological data from three independent cohorts of patients with Alzheimer's disease via next generation sequencing of post-mortem brain tissue.[1] These data showed increased nucleic acids and proteins from human herpesvirus 6A and 7 in four brain regions of patients with Alzheimer's disease compared with healthy controls. The study showed that viral copy number was associated with modulators of the metabolism of amyloid precursor protein. The findings suggest that viral proteins might be working as transcription factors modulating genes in this disorder. However, the causative role of these viruses in the aetiology and pathogenesis of Alzheimer's disease is still highly speculative. The replication of these findings and establishment of animal models of chronic CNS dysfunction caused by herpes virus infections is now warranted.

Treatment is another important aspect of neurological infections and includes the development of a wide range of antibiotics penetrating easily into the meningeal and CNS compartments. However, acute bacterial meningitis still carries a high mortality and long-term morbidity due to delayed presentation, delayed treatment initiation, and a small number of diagnostic facilities. Thus, to improve the course of acute bacterial meningitis, early adjunctive therapeutic strategies, such as neurocritical care and treatment of brain oedema with intravenous dexamethasone, were implemented. A prospective study of 90 patients admitted to a hospital in Ethiopia with diagnosis of acute bacterial meningitis investigated short-term outcomes.[2] Causative bacteria, mainly *Streptococcus pneumoniae* or *Neisseria meningitidis*, were isolated in only 26 (29%) patients, and more than half of the 90 patients had either unfavourable outcomes (33 [37%] patients) or died (20 [22%] patients). Risk factors for increased morbidity and mortality were impaired level of consciousness, dexamethasone therapy, and fever persisting for

more than 2 days after diagnosis. These risk factors led to the conclusion not to administer intravenous dexamethasone routinely for acute bacterial meningitis in poor settings, whereas the best possible neurocritical care, including artificial ventilation and external ventricular drainage, were clearly capable to reduce mortality.

Another issue with important therapeutic implications is the evidence suggesting that patients who had herpes simplex virus encephalitis (HSE) might relapse because of an autoimmune-mediated attack against NMDA or GABA B receptors. A case series of five patients with post-HSE relapsing encephalopathy showed the presence of antibodies in the serum and the CSF against synaptic antigens (ie, NMDA or GABA B receptors) using cell-based assays.[3] The frequency, clinical presentation, risk factors, and prognosis of autoimmune encephalitis were also evaluated by another study,[4] including 51 patients who had HSE. 14 (27%) patients developed autoimmune encephalitis within 2 months after HSE. Signs and symptoms were age-dependent, and children under 4 years of age had the worst neurological outcomes. These findings show the importance of early diagnosis, because adult patients and children older than 4 years can respond to immunotherapy. Thus, the possibility of autoimmune-mediated encephalitis after HSE might carry important therapeutic implications, because immune suppression and modulation might improve prognosis.[4] The best therapeutic regimen should now be explored in clinical trials.

Malaria is a life-threatening disease caused by parasites. Genetic factors are major determinants for malaria risk. A case-control study of 2244 children with severe malaria and 3949 healthy control infants investigated associations between various candidate malaria-protective genes and risk of severe disease.[5] 121 polymorphisms in 70 candidate genes were tested and statistically significant associations between severity risk and polymorphisms in 15 genes were reported. Of particular importance is the significant association between severe malaria and polymorphisms in the genes coding for two antigens, ATP2B4 and the Dantu blood group antigen, that are associated with the structure and function of red blood cells. This finding raises the possibility that these antigens are linked with the resistance of red blood cells to *Plasmodium falciparum* infection. An important aspect of future research will be to elucidate the mechanisms that these antigens use to convey malaria protection.

In the last decade, viral vectors have emerged as tools to deliver genes into human tissues. The arsenal of vectors has increased with the introduction of polio virus for the treatment of malignant glioma. A publication reported the results of a phase 1 dose-finding study of intratumoural delivery of a recombinant non-pathogenic polio-rhinovirus chimera in 61 patients with recurrent gliomas.[6] The vector recognises the poliovirus receptor CD155, which is expressed in neoplastic cells and solid tumours, and induces an immune response that kills these cells. Overall survival reached a plateau of 21% 2 years after treatment, which was sustained at 36 months and was higher at 24 and 36 months than the overall survival in historical controls. Two patients died during the study and at least one death was related with the study intervention. Other adverse effects were headache, hemiparesis, and cognitive disturbances. There was no neurovirulence and none of the patients developed poliomyelitis. A phase 2 study assessing the therapeutic effect of this vector on patients with malignant glioma is underway (NCT01491893).

Although these publications provide important information on the pathogenesis of neurological infections, none brings the respective topic to completion, but they are all parts of an ongoing story that should be pursued till the end.

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