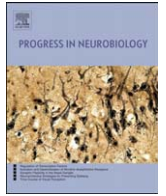


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Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Foreword

Neurobiology of infectious diseases: Bringing them out of neglect

Among the most devastating diseases of the nervous system that plague today's world with a heavy death toll are those caused by infections, such as cerebral malaria, rabies, toxoplasmosis, bacterial meningitis, arbovirus encephalitis and HIV-associated neurological diseases, to name a few. The burden of these diseases is enhanced because survivors may often be left with neurological sequelae affecting motility, sensory organs and cognitive functions, as well as epilepsy. This in turn seriously impairs socio-economic progress in tropical regions of the world where such diseases are particularly prevalent.

Several neuroinfections occur worldwide, whereas others show specific geographical location as they are transmitted by a local animal reservoir or vector. Dozens of parasites, bacteria and viruses can spread to the nervous system (Table 1 provides information on those covered in this issue), causing diseases that are rarely addressed at neuroscience meetings in the Western world with the exception of HIV-associated neurocognitive disorders. In contrast, the neuroscience field has already benefited from concepts and tools developed in study of infections from the first decades of the last century. For instance, the standard diagram of the sensory dermatomes originated from an article on shingles (Head and Campbell, 1900; referred by Johnson, 1982), whereby the herpes zoster virus made a major contribution to neuroanatomy. Studies on propagation of herpes simplex virus predicted axonal transport in anterograde and retrograde directions (Goodpasture and Teague, 1923), providing a basis for the use of various viral strains as tracers to map neural connectivity as well as of viral vectors to deliver genes to the nervous system. Diencephalic areas involved in sleep/wakefulness regulation were first described in studies of patients deceased from *encephalitis lethargica*, emerged during the decade following 1916 (von Economo, 1930). Trypan dyes, initially developed and used by Paul Ehrlich to stain and kill trypanosomes, played a pioneering role in the discovery of and research on the blood-brain barrier (BBB; Goldmann, 1913).

There is no doubt that infections of the nervous system are an important, yet underestimated, cause of neurological syndromes in countries with limited resources for public health systems. WHO has estimated that “about 1 billion people are affected by one or more neglected tropical diseases (NTDs). These diseases are named “neglected” because they persist exclusively in the poorest and the most marginalized populations.” These NTDs include several infections that affect the nervous system such as human African trypanosomiasis, Chagas disease, leprosy and neurocysticercosis (Hotez et al., 2007). Fundamental research on pathogenetic mechanisms of, for instance, cerebral malaria,

bacterial meningitis, vector-borne encephalitis as well as trypanosomiasis, toxoplasmosis, leprosy, rabies and retrovirus infections is mostly carried out by microbe and cell biologists. It is now time to promote interest among neuroscientists to decipher mechanisms underlying microbe-induced nervous system dysfunctions (Bruzzone et al., 2009). For instance, neuroscience could play a crucial role in unraveling molecular mechanisms for uptake, transport and selective targeting of pathogens to neurons after crossing the BBB, in studying the effects of the inflammatory response on synaptic function and homeostasis, in understanding microbial hijacking of neuronal signaling pathways, cognitive impairments, sleep pattern disturbances and neurodegeneration/protection as well as seizures and repair processes following infections.

We are therefore very thankful to the editor of *Progress in Neurobiology* for dedicating this special issue to the field of neuroinfections with a series of reviews based on presentations given at the conference “Infectious diseases of the nervous system: Pathogenesis and worldwide impact,” which was held at Institut Pasteur, Paris, September 10–13, 2008. In the first article, Diane Griffin provides an overview of emerging and re-emerging neurotropic viruses, which are arising when viruses expand their geographic range, spread from animal reservoirs or acquire new neurovirulence properties. Her review addresses the key factors that may explain this occurrence. First, the expansion of viruses to new geographic regions due to modern transportation bringing vectors that efficiently transmit arboviruses into new areas (e.g., the Asian tiger mosquito *Aedes albopictus* into North America and Europe). Second, the spread of viruses into humans from animal reservoirs, with the example of bats that are increasingly recognized as important host for a number of zoonoses, which cause infection of the nervous system (e.g., lyssaviruses, henipaviruses). Finally, genetic mechanisms (reassortment, mutation and recombination) may also be important for virus adaptation. There is still work to be done, however, to explain why the recently emerged strains of West Nile and Chikungunya viruses appear to be more neurovirulent than those previously circulating, and how enterovirus 71 has gained the ability to invade the central nervous system and cause a spectrum of serious neurologic syndromes, including meningitis, encephalitis and paralysis in young children.

The following articles then highlight research on interactions between infectious agents and the nervous system to answer questions on how pathogens may (i) manipulate cellular functions in the nervous system to their own advantage; (ii) target various

Table 1
Pathogens causing infectious diseases of the nervous system.

Pathogen Name	Disease name	Disease frequency/lethality	Regions most affected
<i>Plasmodium falciparum</i>	Cerebral malaria (Transmission: mosquitoes)	1.12 cases/1,000 children/year; lethal in 1/5 children. Less mortality with artemisinin ^A	Sub-Saharan Africa, South East Asia, Latin America
<i>Trypanosoma brucei</i>	Human African trypanosomiasis or Sleeping sickness (Transmission: tsetse flies)	Decreased to ~20,000 cases (2008); 100% lethal if untreated but survival improved with recent drugs ^B	<i>Rhodiense</i> : Acute form in East/South Africa; <i>Gambiense</i> : chronic in West/Central Africa
<i>Taenia solium</i>	Neurocysticercosis: epilepsy, intra-cranial hypertension (Transmission: pig)	Causes ~ 30% epilepsy cases in endemic areas.	Latin America, Africa, India, China, South East Asia
<i>Neisseria meningitidis</i>	Meningitis and its sequelae: edema, hydrocephalus vasculitis & thrombosis	1/1,000 in Africa & 1/10,000 in EC and USA; lethality 10-50% in neonates	Worldwide distribution with highest incidence in Africa.
<i>Mycobacterium leprae</i>	Leprosy	254,000 cases in 2007; 1.4 per 10,000, a large decrease over 20 years	Africa, Latin America, India
Human Immunodeficiency Virus	HIV-associated neurocognitive disorder or dementia; peripheral neuropathy; delayed brain growth and milestones in neonates ^C	10-30% of the ~33 millions AIDS cases, depending on clade and treatment. Dementia in advanced AIDS predicts death	Sub-Saharan Africa, Western world, former Soviet Republics
Japanese encephalitis virus	Encephalitis (Transmission: mosquitoes)	50,000 cases and 15,000 deaths/year	East Asia (India, Southern China)
Chikungunya virus	Encephalopathy (Transmission: mosquitoes; from mother to newborn)	270,000 cases (La Reunion Island, 2006) with 50% acute encephalitis/death in newborns ^D	India (2x10 ⁶ cases in 2006) and Africa (since 1953); South East Asia & Central/East Africa; Italy in 2007

This table lists the neurotropic pathogens covered in this issue. The information provided is based on data from WHO and CDC, as well as the following papers: **A**—Dondorp et al. (2005); **B**—Simarro et al. (2008); **C**—De Baets et al. (2008); **D**—Robin et al. (2008). Parasites (green); Bacteria (red); Viruses (blue).

regions in the brain to cause distinct neurological disorders; (iii) affect various vascular territories to cause dysfunction of the BBB and the brain parenchyma; (iv) cause sleep pattern disruptions, epilepsy and cognitive disturbances.

(i) *Pathogen manipulation of cell functions.* Most pathogens have devised successful strategies to hijack intracellular signaling pathways to their own advantage (Rohwer and Thurber, 2009) and infections in the nervous system are no exception to this evolutionary old phenomenon. In this issue, Anura Rambukkana shows elegantly how a bacterium, *Mycobacterium leprae*, which causes human leprosy, utilizes the neuregulin-ErbB2/ErbB3 associated transduction network in Schwann cells to activate a signaling cascade that leads to demyelination, thereby generating non-myelinating Schwann cells that are highly susceptible to *M. leprae* invasion and promote bacterial survival. Activation of Erk1/2 via a non-canonical pathway maintains the infected cells in a de-differentiated state, thus, preventing remyelination, and a bacterial niche is provided to allow survival within the peripheral nervous system. Clearly, studies on *M. leprae* may be relevant to our understanding of degenerative and regenerative processes in the nervous system.

(ii) *Targeting of viruses to specific regions of the CNS.* A number of factors determine the targeting of intracellular replicating infectious agents in the nervous system. Such factors include the pathways used by pathogens to spread, i.e., via the blood circulation or along peripheral nerves, as well as receptor repertoires and metabolic properties of the target cells. In this issue we have two examples of infections by arthropod-borne viruses (arboviruses), Japanese encephalitis virus (JEV) and Chikungunya virus (CHIKV), which cause lesions in the brain with remarkable differences in their localization. From its origin in Japan, JEV has spread westwards and reached India, as reviewed by UK Mishra. It is a neurotropic virus, which mainly affects the striato-nigral system, thalamus, and lower motor neurons. CHIKV, causes arthritic pain and has not been considered a “true” neurotropic virus like West Nile virus, which is causing seasonal outbreaks in the US since 1999 (Davis et al., 2006), but in a recent outbreak at La Reunion in the Indian Ocean a substantial number of

patients showed abnormal MRI scans (Robin et al., 2008; see also the article by Gasque et al. in this issue). The two articles give a comprehensive review of these emerging infections and emphasize the large gaps in our knowledge of their neuropathogenesis. Since they affect regions of the nervous system that are involved in certain neurodegenerative disorders, these infections would benefit from collaborative research with neuroscientists.

(iii) *Pathogen interactions with different meningo-cerebrovascular territories.* Although some viruses, such as herpes simplex and rabies viruses, can propagate along peripheral nerves, most pathogens reach the brain via blood circulation and encounter the BBB, which generally excludes their entry into the brain. However, as described here by Join-Lambert and Nassif, *Neisseria (N) meningitidis*, which first colonizes the human oropharyngeal or digestive mucosal barrier, later reaches the bloodstream and eventually crosses the vessels in the meninges. Entry of *N. meningitidis* requires the participation of the actin cytoskeleton via the activation of both Rho and Cdc42 Rho GTPases, which lead to the formation of cellular protrusions (i.e., filopodia) that promote efficient bacterial uptake. Of note, this signaling cascade is similar to that triggered by leukocyte adhesion on endothelial cells. This is another example of neurotropic pathogens hijacking the cellular machinery normally used for trans-endothelial migration of endogenous cells. A closer look at this process may provide clues on how to restrict crossing of the meningeal vessels or an unwanted inflammatory reaction. Some pathogens, like HIV, can cross the BBB to invade the brain parenchyma inside white blood cells. Others, like *Plasmodium falciparum*, do not traverse this barrier. Two million African children die each year of severe malaria, mainly due to anemia and cerebral malaria (CM). Combes et al. describe in their review how red blood cells parasitized by *P. falciparum* preferentially get sequestered in the cerebral microvasculature by binding to ICAM1 and other adhesion molecules on activated endothelial cells. Intravascular macrophages releasing cytokines, platelet aggregation and the accumulation of microparticles further aggravate this sequestration leading to cerebral hypoxia, hemorrhages and edema, which contributes to the

clinical signs of CM. Authors discuss how some malaria antigens and cytokines may enter the brain parenchyma and induce microglial activation and/or astrocyte death, ultimately leading to neuronal damage, and how brain dysfunction is correlated with changes in gene expression.

(iv) *Pathogens and sleep pattern disruptions, epilepsy and cognitive disturbances.* Several pathogens may target neurons and other neural cells, causing cell destruction and loss of function while others may not kill neurons but interfere with neuronal function at ion channel or synaptic level. This issue contains three reviews on infectious agents causing sleep disruption, epilepsy and cognitive disturbances, respectively: *Trypanosoma brucei* (*Tb*), *Taenia solium* and HIV.

Subspecies of *Tb* cause human African trypanosomiasis (HAT) – also called sleeping sickness – which is different from *encephalitis lethargica*, described by von Economo, whose etiology is still a mystery. The extracellular trypanosomes are transmitted by tsetse flies prevalent in sub-Saharan Africa. By localizing to basal meninges and circumventricular organs around the third ventricle, the extracellular trypanosomes may cause release of molecules that affect the function of neurons in the basal forebrain and diencephalic nuclei which are involved in the regulation of sleep/wakefulness and circadian rhythms. It is of special interest that the balance between sleep-promoting and wake-promoting circuits appears sensitive to the inflammatory signals which are the hallmarks of *Tb* infection. The complexity in interactions between immune response molecules on one hand, and sleep homeostasis and circadian rhythms on the other is a major challenge for future studies.

In their review on neurocysticercosis, a zoonosis, Mahanty and Garcia describe how *T. solium* can persist for a long time in different organs and cause seizures when viable cysts have developed in the brain parenchyma. More dramatic is the growth of the parasite in subarachnoidal spaces causing progressive hydrocephalus and intracranial hypertension. The authors first cover in detail the parasite cycle and then describe the diagnostic tools, the multiple faceted treatment and outcome of different clinical presentations as well as the Th1 and macrophage response leading to granuloma formation and epilepsy. Importantly, they discuss the logical prevention strategy to eliminate the *Taenia* larval population from pork farms in Peru. However, this threatens the income of poor peasant communities in endemic regions. The latest strategy is to perform pig vaccination while treating both pigs and infected people with antiparasitic drugs with the goal to eliminate disease in Latin American countries as was done in Europe.

In contrast to the other infections of the nervous system described in this issue, the neurocognitive impact of HIV has received considerable attention in the Western world. Ellis now describes the recent systematic research also on the large HIV positive populations in Africa and Asia. There has been speculation that the neurocognitive disorders seen in Western populations may be attributable to comorbidities such as recreational drug use and other factors. However, it is becoming clear from studies done in these other regions of the world that neurocognitive impairments of similar type and degree affect HIV+ individuals despite the absence of these comorbidities. The neuropathological substrate of HIV neurocognitive disorders resides in alterations in synapses and dendrites, without major neuronal loss. Some degree of recovery following combination antiretroviral therapy (CART) is universal and this treatment has resulted in the near disappearance of AIDS dementia. The ability to restore integrity of synapses and dendrites is of fundamental research interest, since they are early targets in prevalent neurodegenerative diseases. As pointed out by Ellis, key questions concerning HIV infections

of the brain in the era of CART therapy include: (a) Does chronic infection of the CNS by HIV lead to irreversible neural injury? (b) What is the full extent of neuronal recovery that may be expected with CART? (c) Can this recovery be facilitated and further injury prevented?

Although prevention strategies, e.g., vector control, improved hygiene and vaccinations, and treatment by newly developed drugs are the key elements in combating neuroinfections, novel neurotropic pathogens will arise with environmental changes or re-emerge as is the case with poliomyelitis. Infections involving the brain raise specific questions in which neuroscience research could play an important role, for example, in determining neurovirulence factors of pathogens and disease specific markers of infection. More efforts are needed to develop treatment of neural tissue dysfunctions during acute and chronic infections, design ways to prevent functional or structural sequelae, as well as determine the effects of early infections on synaptic formation and neuronal function in various regions of the brain later in life. In addition, functional genomics applied to diverse types of infections could help unravel molecular mechanisms by which defined pathogens cause dysfunction or degeneration of the nervous system. This, in turn, might contribute to our understanding of the pathogenesis of neurodegenerative and neuropsychiatric disorders of unknown etiology.

We hope that fundamental research in neuroscience will combine with microbiology to foster rapid advances and close gaps in knowledge on the pathogenesis of these most prevalent, yet too often neglected diseases of the nervous system. Since the first conference on infectious diseases of the nervous system was held at Institut Pasteur in Paris and there is a strong pressure for applied research in this field, a quote by Louis Pasteur seems appropriate: “*il n’y a pas de recherche appliquée, il n’y a que des applications de la recherche fondamentale*” (there is no applied research, there is only applications of fundamental research) (<http://www.retina.fr/ret53-fondamental.html>). This should inspire neuroscience researchers to collaborate with microbiologists to enhance discoveries and applications in the neuroinfection field.

References

- Bruzzone, R., Dubois-Dalcq, M., Grau, G.E., Griffin, D.E., Kristensson, K., 2009. Infectious diseases of the nervous system and their impact in developing countries. *PLoS Pathog.* 5, e1000199.
- Davis, L.E., DeBiasi, R., Goade, D.E., Haaland, K.Y., Harrington, J.A., Harner, J.B., Pergam, S.A., King, M.K., DeMasters, B.K., Tyler, K.L., 2006. West Nile virus neuroinvasive disease. *Ann. Neurol.* 60, 286–300.
- De Baets, A.J., Lepage, P., Ramet, J., Mujuru, H., Savadogo, L.G., Van der Linden, D., Bulterys, M., 2008. Using a sociological model to analyze access to pediatric HIV/AIDS care in rural sub-Saharan Africa. *Curr. HIV Res.* 6, 563–571.
- Dondorp, A., Nosten, F., Stepniewska, K., Day, N., White, N., South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group, 2005. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 366, 717–725.
- Goldmann, E.E., 1913. *Vitalfarbung am Zentralnervensystem.* Eimer. Vitalfarbung am, Berlin, 1913.
- Goodpasture, E.W., Teague, O., 1923. Transmission of the virus of herpes febrilis along nerves in experimentally infected rabbits. *J. Exp. Med.* 44, 139–184.
- Head, H., Campbell, A.W., 1900. Pathology of herpes zoster and its bearing on sensory localization. *Brain* 23, 353–523.
- Hotez, P.J., Molyneux, D.H., Fenwick, A., Kumaresan, J., Sachs, S.E., Sach, J.D., Savioli, L., 2007. Control of neglected tropical diseases. *N. Engl. J. Med.* 357, 1018–1027.
- Johnson, R.T., 1982. *Viral Infections of The Nervous System.* Raven Press, New York.
- Robin, S., Ramful, D., Le Seach, F., Jaffar-Bandjee, M.C., Rigou, G., Alessandri, J.L., 2008. Neurologic manifestations of pediatric chikungunya infection. *J. Child Neurol* 23, 1028–1035.
- Rohwer, F., Thurber, R.V., 2009. Viruses manipulate the marine environment. *Nature* 459, 207–212.
- Simarro, P.P., Jannin, J., Cattand, P., 2008. Eliminating human African trypanosomiasis: where do we stand and what comes next? *PLoS Med.* 5, e55.
- von Economo, C., 1930. Sleep as a problem of localization. *J. Nerv. Ment. Dis.* 71, 249–259.

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9 February 2009