Acta Neuropathol (2016) 131:155–158
DOI 10.1007/s00401-016-1535-3

EDITORIAL

Re-emergence of neuroinfectiology

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Published online: 11 January 2016

Introduction

Infections of the central nervous system (CNS) represented an area of major concern in the pre-antibiotic and pre-vaccination era. Following the wide-spead introduction of antibiotic therapy and the implementation of national vaccination programs, many infectious diseases appeared to be successfully contained, and the health threat posed by infectious pathogens seemed to belong to the past. However, in recent years the number of reported cases of infectious agents causing CNS infections in the form of emerging and re-emerging diseases has been increasing [9]. Among the most devastating infectious diseases of the CNS that plague today's world are cerebral malaria, rabies, toxoplasmosis, bacterial meningitis, arbovirus encephalitis and human immunodeficiency virus-associated neurological diseases [4, 5, 9, 20–22]. Viral and bacterial CNS diseases represent an important but relatively neglected area of medicine in developing countries [8]. Similarly, parasite-inflicted diseases of the CNS represent a major threat to public health indeveloping countries; this threat is also present in the Western world but the disease burden is less [4, 5]. Overall, the burden of infectious CNS diseases is reinforced by the fact that survivors may suffer from life-long lasting neurological and psychiatric complications [1, 15, 24, 25].

Neuroinfectiology as per definition

The most obvious sensu stricto definition of neuroinfectiology refers to a direct pathogen–host cell effect resulting in cytolysis and inflammation. The host cell–pathogen interaction is most frequently discussed in the context of a black-and-white response, namely, as cell death or cell survival. However, especially in the CNS, cellular functions may remain impaired despite cell survival. A reduction of cellular "luxury functions", which is defined as a loss of key elements that are essential to maintain organ homeostasis, may result in impaired organ function. A pathogenic infection will not only have direct effects upon a host's cells, but it may also have extensive indirect consequences on the host organism that may include the derailment of responses, including autoimmunity, epitope spreading, molecular mimicry and genetically-mediated susceptibility, as well as detrimental interactions with non-infectious environmental factors. Predisposing factors, such as diabetes mellitus, malignancies, inherited immune deficiencies, deprived immunity in the elderly, immunosuppression due to therapies (cancer, organ transplantation) and/or pathogens, may enhance a potential host's susceptibility for an infection. Therefore, a broader definition of neuroinfectiology should include the predisposing mechanisms, acute host–pathogen interactions, as well as the long-term, delayed disturbances and disabilities (degeneration, malformation, sensory or motor deficits, cognitive impairment, behavioral changes and epileptic seizures) that may occur immediately or years after the initial infectious process [1, 15, 25]. Detailed investigations of such consequences require a multidisciplinary effort by experts from various fields to determine the

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etiology, discover the underlying mechanism and design prevention and intervention strategies.

The cause of an inflammatory CNS disease frequently remains undetermined. Approximately 30 % of patients with suspected CNS infection lack an etiological diagnosis and one-third of these patients ultimately die as a result of the illness [19]. However, present-day researchers have acquired a new diagnostic tool, namely, metagenome sequencing, and this tool is increasingly being applied to the identification of pathogens [18]. Intensified search with this tool and with new technologies have resulted in the identification of various pathogen vectors, including bats, domestic pets and wildlife animals, for different agents, such as the Hendra and Borna viruses, Japanese encephalitis infection and Middle East respiratory syndrome (MERS) coronavirus [7, 8, 10, 21].

Neuroinfectiology, pathogens and epilepsy

This issue of *Acta Neuropathologica* includes a cluster of three review articles on neuroinfectiology with special emphasis on viral and bacterial diseases as well as the role of these diseases in epilepsy [6, 13, 23]. These reviews reflect the plethora and diversity of causes, consequences and reaction patterns in neuroinfectiology.

The review by Ludlow et al. [13] depicts emerging and re-emerging neurotropic and non-neurotropic viruses that cause CNS diseases and sheds some light on the mechanisms underlying both the direct and indirect as well as the immediate and delayed consequences of these diseases. Viral diseases of the CNS, many arising from zoonotic pathogens, can be caused by a variety of viruses, including the bunyavirus, Nipah virus, Hendra virus and rabies, polio, tick-borne encephalitis, herpes and measles viruses [7, 9, 21, 22]. Viral CNS infections are commonly caused by mosquito-borne viruses, such as the West Nile, Chikungunya and Japanese encephalitis viruses, which have in recent times expanded their geographic range. In addition, some viruses, including the bat henipaviruses Nipah virus and Hendra virus, the Borna virus as well as the Japanese encephalitis virus, have crossed the human species barrier (spill-over infection) [10, 21, 22].

Various bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, enterohemorrhagic *Escherichia coli* (EHEC) and *Listeria monocytogenes*, are among the most common bacterial causes of CNS diseases in humans. Others, such as *Streptococcus suis*, are zoonotic pathogens with great regional differences as formidably described by the review of Doran et al. [6]. In Africa's so-called "meningitis belt", which stretches from Senegal to Ethiopia, outbreaks of meningitis due to meningococcal disease caused by *Neisseria meningitidis* occur regularly, killing thousands and infecting tens of thousands each year [20]. Complications and long-term sequelae after the initial bacterial infection include epileptic seizures, hydrocephalus, infarction, herniations and persistent defects after healing. Noteworthy, septic patients may develop septic encephalopathy, a potentially irreversible acute cerebral dysfunction which is clinically characterized a slowing of mental processes, impaired attention, memory dysfunction, delirium and/or coma [24].

Epilepsy with recurrent unprovoked (spontaneous) seizures may be a serious consequence of CNS infections [23]. The current terminology for the concept(s) and underlying cause(s) of epilepsy refers to three categories, i.e. genetic, structural/metabolic and unknown. This categorization replaces the previously used terms of idiopathic, symptomatic and cryptogenic. Epilepsy resulting from various processes, including traumatic brain injury, neoplasms, ischemic or hemorrhagic stroke and CNS infection, belong to the structural/metabolic category. Congenital and developmental issues and genetic conditions are mostly associated with the development of epilepsy in younger patients, whereas infection, head trauma and tumors leading to epilepsy may occur at any age. In survivors of CNS infections, the risk of unprovoked seizures is approximately 7 % in developed countries, but much higher in resource-poor countries. In their review, Vezzani et al. [23] comprehensively describe the infectious diseases and sterile (non-infectious) inflammatory responses, as well as the associated underlying complex pathogenetic mechanisms, which result in the development of epilepsy. These authors also describe those factors which play a critical role during epileptogenesis and which should be considered in prevention strategies.

Long-term consequences, contributing factors and new concepts

The causes of degenerative, inflammatory and behavioral disorders, including Alzheimer disease, Parkinson disease, multiple sclerosis, Guillain–Barré syndrome, encephalitis lethargica, congenital malformations, schizophrenia and bipolar disorder, are largely unknown. However, recent studies have been (re)-focusing on the role of neuroinflammation and infections as driving forces. In addition, new concepts in which infections early in life are considered to be predisposing factors with clinical manifestation(s) decades later are now being studied [11, 13–15].

Factors contributing to the emergence of new pathogens include changes in human demographics and behavior, intensification of international travel (tourism), commerce (global trade), increased economic development and land use, increasing importation of infected animals and exotic pet trade and the altered migration of vectors (such as birds and arthropods) and their adaption in new environments,

in part facilitated by global warming [9, 17]. Faced with complex patterns of global changes, the researcher analyzing the interconnections among humans, companion animals, livestock and wildlife requires integrated approaches. These complex interactions and their conceptual interpretation depend on a multidisciplinary and cross-sectoral approach involving experts in both human and veterinary medicine as well as those in ecology, as envisioned by the One Health–One Medicine concept [12, 26].

In addition to opportunistic infections, activation of silent—primarily non-pathogenetic—agents may represent a future threat as potent drugs are available to treat autoimmune disease, organ transplants and cancer. In addition, more patients with congenital immunodeficiency live longer and may be exposed to these pathogens. Similarly, the gut microflora has been shown experimentally to play an important role as a trigger of CNS inflammation [3]. Furthermore, T cells become licensed in the lung to enter the CNS [16]. These different modes of pathogen–host or immune system interaction may represent future avenues by which to study the pathogenesis of inflammatory and degenerative lesions in the nervous system, as outlined in the recent review by Bauer et al. [2] which focuses on progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome.

Conclusions

Neuroinfectiology represents an emerging multidisciplinary field which centers on the complex interactions between CNS and pathogen-associated cellular and molecular processes, inflammation, immune responses, degeneration, stem cell homeostasis as well as tissue repair and regeneration. In order to combat this challenge extensive cross-fertilization between scientists from various fields is needed. New pathogens associated with CNS involvement have emerged in recent years. These represent a major threat to public health, are of great economic relevance and represent a medical challenge due to the lack of appropriate diagnostic and treatment strategies [9]. Global trading, tourism and ecological and demographic changes will contribute to outbreaks of diseases due to these emergent agents. Globalization of human travel and industrial exchange facilitates the spread of infections worldwide within a short time period. In addition, developments of immunomodulatory drugs to treat immune-mediated disease might cause opportunistic infections or activation of latent agents. New molecular detection systems will improve our ability to rapidly diagnose and recognize emerging and re-emerging pathogens and the host genetic factors involved in disease susceptibility, but the development of new strategies for diagnosis, prevention and treatment of neurological disorders will only be efficiently addressed by an interdisciplinary approach bridging the fields of neuroscience and infection medicine. Moreover, little is known about the role of pathogen-related predisposing factors, mechanisms causing acute disease in individuals and factors resulting in long-term CNS disturbances. Overall, a more conceptual understanding of neuroinfectiology is pivotal for the development of successful prevention and treatment strategies. Future studies in neuroinfectiology will address questions relating to the mechanisms of direct and indirect as well as acute, delayed and long-term damage, the role of misdirected immune responses in lesion initiation and the progression as well as prevention of CNS infection by developing appropriate intervention strategies and potential beneficial approaches for tissue regeneration.

Acknowledgments The research underlying this editorial was in part supported by Niedersachsen-Research Network on Neuroinfectiology (N-RENNT) of the Ministry of Science and Culture of Lower Saxony, Germany.

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