The Mechanisms of Direct, Virus-Induced Destruction of Neurons

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1 Introduction

The mature neuron is a highly specialised, irreplaceable, post-mitotic cell and neuronal death leaves a permanent deficit. Therefore, irrespective of the cause, any extensive neuronal loss will have profound, if not fatal, consequences for the organism as a whole. The central nervous system (CNS) in humans and all higher orders of the animal kingdom is normally protected by both anatomical barriers and systemic physiological barriers of innate and specific immunity. A limited number of viruses have evolved strategies to penetrate these defences and to gain access to neurons that may result in direct neuronal destruction. However, the outcome of any infection is determined by the interplay between the tactics of the invader and the host response and this balance is equally relevant to viral infection of the CNS. This chapter will concentrate upon herpes simplex virus (HSV) encephalitis, which is still the commonest cause of sporadic acute encephalitis in immunocompetent individuals living in temperate parts of the world. In naturally occurring disease it is rarely possible to dissociate completely the direct cytopathic effects of the virus from cellular injury inflicted by the host immune system, but animal experiments that allow manipulation of certain facets have helped to elucidate the complex interactions and the mechanisms of neuronal destruction. Other chapters will deal more extensively with neurotropism but it will also be considered here in as much as a portal of entry into the CNS, together with susceptibility of CNS cell populations to permissive infection, are the essential prerequisites of virally mediated neuronal destruction.

2 General Histopathological Features of Acute Viral Encephalitis

In the peripheral nervous system several neurotropic viruses achieve latency, but in the immunocompetent host acute permissive viral infection of the CNS invariably results in neuronal lysis and elicits a stereotyped response, which involves microglial activation, neuronophagia and perivascular cuffing with lymphocytes and some plasma cells. Whilst different forms of acute viral encephalomyelitis are not readily distinguished by the character of the inflammatory changes, the geographical distribution within the CNS may provide diagnostic clues. It has been frequently hypothesised that distribution reflects selective vulnerability of certain neuronal populations, but more often it would appear simply to highlight a portal of entry into the CNS. Viruses that reach the CNS via a haematogenous pathway and penetrate the blood–brain barrier are likely to be widely distributed, whereas viruses which travel along nerves follow neuroanatomical pathways, at least initially. The early spinal neuronal involvement in most cases of rabies is attributable to axonal transport and entry via the spinal motor nerves supplying peripheral muscles. Likewise, the apparent susceptibility of anterior horn cells to