Herpes Simplex Virus Infections of the Central Nervous System
Encephalitis and Neonatal Herpes

Richard J. Whitley
Department of Pediatrics, Microbiology, and Medicine, The University of Alabama at Birmingham, Birmingham, Alabama, USA

Contents

Summary
1. History
2. Herpes Simplex Encephalitis
2.1 Epidemiology
2.2 Pathogenesis
2.3 Pathology
2.4 Immunity
2.5 Diagnosis
2.5.1 Clinical Presentation
2.5.2 Brain Biopsy
2.5.3 Serology
2.5.4 Diseases that Mimic HSE
2.6 Therapy
2.6.1 Drug of Choice
2.7 Future Therapeutic Directions
3. Neonatal Herpes Simplex Virus Infections
3.1 Pathogenesis
3.1.1 Acquisition of Infection
3.1.2 Factors Which Influence Transmission of Infection to the Fetus
3.2 Pathology
3.3 Immunity
3.4 Clinical Presentation
3.4.1 Intrauterine Infection
3.4.2 Disseminated Infection
3.4.3 Encephalitis
3.4.4 Skin, Eye and/or Mouth Infection
3.4.5 Diagnosis
3.5 Treatment
3.5.1 Vidarabine Trials (1973 to 1983)
3.5.2 Vidarabine Versus Aciclovir Trial (1983 to 1987)
3.6 Prevention
4. Drug Therapy Recommendations
5. Conclusion
Summary

Herpes simplex virus (HSV) infections are among the most commonly encountered in humans. Fortunately, the resulting diseases are more usually nuisances, such as recurrent fever blisters, rather than life threatening or morbidity inducing. Nevertheless, HSV can result in disease of the central nervous system (CNS) with attendant neurological complications. Examples of the latter include herpes simplex encephalitis (HSE) or neonatal HSV infection. The past decade has witnessed significant advances in our understanding of the pathogenesis of these 2 forms of disease and, even more importantly, their amenability to treatment. This review summarises our current understanding of the natural history, pathogenesis, presentation, and treatment of HSV infections of the CNS.

Because of the life-threatening nature of herpes simplex infections of the CNS, particular attention is paid to clinical presentation and differential diagnosis of confounding entities which mimic herpes simplex encephalitis. The controversy of brain biopsy versus alternative noninvasive diagnostic procedures is discussed. Clinical presentation and, importantly, the lack of uniform clinical presentation, as well as the value of intervention with appropriate antiviral drugs such as aciclovir and vidarabine (adenine arabinoside, ara-A) are stressed. The clinical outcome of herpes simplex virus infections of the CNS with therapy is particularly relevant. In spite of early intervention with selective and specific inhibitors of viral replication, return to normal function is not always achieved. At the conclusion of this review, the reader should be aware of the potential value of therapy as well as the problems encountered with diagnosis and management of patients with herpes simplex virus infections of the CNS.

1. History

The infectious nature of herpes simplex virus (HSV) was first delineated by demonstrating passage of the virus from lip and genital lesions of humans to either the cornea or the scarified skin of the rabbit (Gruter 1924). Goodpasture (1925) demonstrated that the inoculation of vesicular fluid from the lesions of herpes labialis onto scarified cornea of rabbits consistently produced herpes simplex encephalitis (HSE). Intranuclear inclusion bodies consistent with HSV infection were first demonstrated in the brain of a baby with encephalitis in 1941. Since HSV was isolated from brain tissue, this case provided important evidence that HSV can cause encephalitis in a newborn (Smith et al. 1941). The first adult case of HSE with similar findings, i.e. intranuclear inclusions in brain tissue and virus isolation, was described by Zarafonitis et al. (1944). The most striking pathological finding in this case was evidence of perivascular lymphocytic cuffing and numerous small haemorrhages localised to the left temporal lobe – a characteristic pathophysiological event in HSE.

In 1952, Zuelzer and Stulbery reviewed 8 cases of disseminated HSV infection in neonates, with involvement of most organs, including the brain (Zuelzer et al. 1952). Until this time it had been almost axiomatic that newborns were not susceptible to HSV infection. Their report was the first describing visceral lesions definitively attributable to HSV infection. They correctly implicated haematogenous spread of virus as the pathogenic mechanism. Furthermore, they postulated that maternal antibody was not protective, that infants born to mothers with herpetic lesions were at special risk, and that exposure after birth may lead to infection. Recognition of HSV as a cause of encephalitis progressed to such an extent that in a 1960 review of CNS viral syndromes (Meyer et al. 1960), HSV was the third most frequent cause of encephalitis.

In the mid 1960s, Nahmias and Dowdle demonstrated 2 antigenic types of HSV, HSV-1 and HSV-2. This distinction led to the definition of the epidemiology of HSV infections. Viral typing allowed demonstration that HSV-1 is primarily responsible for herpes infections ‘above the belt’ while HSV-2 causes herpes infections ‘below the belt’ (Nahmias & Dowdle 1968). Over the past 15 years, knowledge of the molecular biology of HSV has expanded, especially regarding the biochemistry of viral replication and associated gene products as