Herpes encephalitis

II. Pathology of herpes encephalitis

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Summary

Herpes simplex infection of the CNS may occur as part of a generalized infection with visceral involvement or with the CNS alone involved. Aseptic meningitis due to herpes simplex is rare, but necrotizing encephalitis is being recognized with increasing frequency.

The distribution of lesions within the CNS and the mode of spread to and within the CNS are discussed.

Serological tests indicate that some cases are due to primary infection and others due to re-activation.

The importance of early diagnosis by electron and fluorescence microscopy and virus culture are discussed.

The natural history and pathogenesis of herpes simplex and B virus are discussed.

Introduction

The herpes viruses comprise a composite group of infectious agents which are widely distributed in nature amongst different animal species. Some of the more important members of the group are shown in Table 1.

The herpes viruses are all DNA viruses and those that have been studied by electron-microscopy have a cubic symmetry with 162 capsomeres (Andrewes, 1964). Their size is about 100–150 mμ. There are serological cross-reactions between several members of the group but individual strains are closely related antigenically. Under natural conditions these viruses exhibit a marked species specificity, but in the

laboratory they can be made to infect a wide range of experimental animals and cell cultures. Several herpes viruses may produce neurological disease. This includes disease contracted as part of a natural infection, as for example in herpes simplex, varicella-zoster and pseudo-rabies, or from disease following an accidental infection, as for example B virus infections in man.

In human medicine, the two most important viruses which are capable of causing severe CNS disease in man are herpes simplex and B virus, its simian counterpart.

Herpes simplex encephalomyelitis (*Herpesvirus hominis*)

Natural history and epidemiology

This virus is one of the most common of all viral agents infecting the human race. This is revealed from serological studies which show that herpes antibody is widely distributed throughout the populations of the world. Herpetic infections are of two main types, primary and recurrent. Both types of infection are distinct and both may be important in the pathogenesis of infections of the central nervous system.

(a) Primary infections occur in individuals without previous immunity and as a result specific neutralizing antibody develops. Primary infection, which is frequently inapparent, commonly occurs in childhood after maternal antibody has disappeared, but it may be, and frequently is, delayed until adult life owing to the changing environmental conditions in

TABLE 1. Herpes group of viruses

Proper name	Synonym	Common name	Natural host
<i>Herpesvirus hominis</i>	Herpes febrilis, labialis	Herpes simplex	Man
<i>Herpesvirus varicellae</i>	Varicella-zoster	Chickenpox and shingles	Man
<i>Herpesvirus simiae</i>	B virus	–	Monkeys
<i>Herpesvirus suis</i>	Aujeszky's disease	Pseudo-rabies, mad itch, infectious bulbar paralysis	Cattle, sheep, pigs
<i>Herpesvirus ciniculi</i>	Virus III	–	Rabbits

many countries. Following primary infection the virus is not completely eliminated but a state of latent infection ensues.

(b) Recurrent infections occur in individuals who have previously been infected and who possess circulating antibody. They are seen more commonly in adults and result from reactivation of latent virus. It is unlikely that re-infection is of much consequence in recurrent herpes. Lesions are commonly found on the skin or muco-cutaneous borders on the face, particularly in the area supplied by the second and third divisions of the fifth nerve, on the skin and mucous surfaces around the external genitalia and on other areas of skin at the site of primary infection. Individuals subject to recurrent herpes often develop herpes at precisely the same site on the skin. This is also commonly seen in recurrent corneal herpes. The factors responsible for the recurrence of herpetic eruptions are not known. In many individuals there appears to be some trigger mechanism such as fever, a cold or some other respiratory infection, sunlight or menstruation, but in many individuals no such inciting cause can be elicited. At the time of a recurrence, infectious virus can be recovered from the cutaneous lesions, but in between attacks virus apparently disappears from these areas and presumably remains in a latent and non-infectious form. The site of this is not known; it may be in ectodermal cells in the skin or in the mouth or in nerve endings. The relationship between recurrent herpes and trigeminal neuralgia is of special interest in this connection. Patients with trigeminal neuralgia sometimes suffer from recurrent herpes, and more frequently crops of vesicles may develop 2-3 days following operation for relief of pain along the course of the divided nerve. This could be explained on the basis that virus was latent in the Gasserian ganglion or nerve and was re-activated by trauma.

Herpes simplex is transmitted from one person to another by direct contact with the skin or mucous surfaces. Sources of infection are secretions of the mouth, eye and genitalia from individuals with active herpes, particularly recurrent labial herpes, and from asymptomatic carriers. Approximately 5% of apparently healthy individuals carry herpesvirus in their saliva. Herpes antibody is widespread in most adult populations and as a result most women have acquired infection by the age of child-bearing. Antibody of the IgG type passes across the placenta from the mother and confers passive protection on the child in the early weeks of life. After this has disappeared by about 6-9 months of age the child becomes fully susceptible, but primary infection seldom occurs until about 18 months to 2 years of age except for those at special risk, for example premature infants and infants with eczema. By the age of 5 years 10% of children are found to possess

antibody and by 15 years 75%. Infection is acquired earlier in the lower socio-economic groups or wherever overcrowding occurs. Once acquired antibody is maintained throughout life. Little difference can be detected in antibody levels of patients who have experienced clinical as opposed to subclinical infections or in patients who suffer from recurrent attacks of herpes.

Pathology and pathogenesis

The characteristic lesion of herpes simplex whether it is in the skin, liver, adrenals or brain is one of cell necrosis associated with intranuclear changes consisting of margination of the nuclear chromatin and development of intranuclear inclusions. Cell necrosis may be focal or massive. In the skin, cell necrosis leads to vesicle formation; in the brain to destruction of nerve cells and supporting structures.

Herpesvirus probably enters the body through small abrasions in the skin or mucosae, or by direct inoculation caused by trauma. After initial local multiplication, virus passes to the regional group nodes and may then pass to the blood stream from which it may spread to other organs. Virus multiplication may be halted at any stage by the body's defence mechanisms. In recurrent herpes, infection is more restricted; often the same area of skin or mucosa is repeatedly involved. It is probable that virus passes from one infected cell to another, being restricted from more general spread by the presence of circulating antibody. Under certain conditions virus may spread to cause more extensive disease.

CNS infections

Involvement of the CNS may occur as a result of either primary or recurrent infection, but a precise delineation between the two forms is not possible without appropriate laboratory tests. In cases where encephalitis is associated with cutaneous lesions and a disseminated visceral infection, it can be presumed that these have resulted from primary infection, but in older patients and children with CNS symptoms only it is difficult to determine whether infection is primary or results from reactivation. The following types of herpetic infection of the CNS have been recognized:

- (i) Aseptic meningitis
- (ii) Acute encephalomyelitis with or without visceral necrosis
- (iii) Acute necrotizing encephalomyelitis.

Aseptic meningitis

Reports in the 1940s suggested that herpetic meningitis was by no means uncommon. This view is not held today. Some appeared to be recurrent

and some followed lumbar puncture (Janbon, Chaptal & Labraque-Bordenave, 1942). As herpes-virus is such a common infectious agent and can be recovered quite readily from the saliva of apparently healthy individuals, great care must be taken in the interpretation of reports of isolation of the virus from spinal fluid particularly when the CSF shows no abnormality. Armstrong (1943) reported the isolation of herpes simplex virus from the spinal fluid of a case of aseptic meningitis and suggested that herpes was one of the causal agents of the aseptic meningitis syndrome. Laboratory studies reported by Macrae (1961) in this country indicate that herpes is a rare cause of aseptic meningitis. In a recent survey of fifty-two cases of herpetic involvement of the CNS Leider and his colleagues (1965) encountered three cases of meningitis, one in a girl of 15 and two in adults. A recent review by Olson and his colleagues (1967) records ten cases of aseptic meningitis in a retrospective study of forty-nine cases of CNS disease associated with herpes simplex infection. Clinically these ten cases were indistinguishable from aseptic meningitis due to other viruses.

Acute encephalitis with or without visceral necrosis

This severe type of fulminating infection is in the main confined to infants under 1 year of age and is of special consequence in premature infants in the newborn period. Other predisposing causes are infantile eczema and severe protein malnutrition. Hass (1935) first described a case of hepato-adrenal necrosis in a premature infant and because of the intranuclear inclusions this was ascribed to herpes simplex. In 1941, Smith, Lennette & Reames (1941) reported the isolation of herpesvirus from the brain of a 4-week-old infant who died of an acute encephalitis. Zuelzer & Stulberg (1952) reported five cases of fulminating herpes simplex infection in the newborn. All were premature by weight and had extensive visceral necrosis. Herpesvirus was recovered from the brain of three of these patients, but encephalitic symptoms were not a marked feature in these fulminating cases. Haymaker and his colleagues (1958) summarized the findings of nine cases of acute encephalitis in infants under 1 year; in two there were accompanying visceral lesions and in several the lesions were confined to the central nervous system.

Acute necrotizing encephalomyelitis

The first report of this type of case, presenting usually in adults, but occasionally in children and adolescents, without clinical manifestation of involvement of other systems, was made by Van Bogaert, Radermecker & Devos (1955). Later further cases were reported by Haymaker and colleagues

(1958) and in the past 5 years further reports have appeared (Leider *et al.*, 1965; Adams & Jennett, 1967; Harland, Adams & McSeveny, 1967). Altogether over 100 cases have now been recorded.

The pathology of herpetic infection of the CNS

The pathological changes in cases of aseptic meningitis are not known as few cases, if any, have come to autopsy. The morbid-anatomical changes in cases of acute encephalitis in both infants and adults are similar but differ in the severity of the necrosis. In the infantile group there is usually such gross softening that the brain is semi-liquid at autopsy. Haemorrhages are found throughout the brain being marked in cortical areas, basal ganglia and brainstem. In adults there is usually softening which is generally asymmetrical, with numerous small haemorrhages on the surface of softened tissue. Histologically the characteristic lesion is one of acute haemorrhagic necrotizing encephalitis. The lesions are widespread, bilateral and asymmetrical. Areas most commonly affected are the temporal and orbital gyri, the insulae and the cingulate gyri. The necrotic areas in the cortical grey matter tend to be well demarcated with some spread into the adjacent white matter. Meningeal cellular exudate and perivascular cuffing with neuronophagia is found in necrotic areas. Intranuclear inclusions are found in neurones and microglia but their presence is extremely variable.

The appearances of a fairly typical case of herpes necrotizing encephalitis in a 13-year-old girl from which the virus was recovered at autopsy (Blackwood *et al.*, 1966) is shown in Fig. 1.

FIG. 1. Hemi-section of brain of a 13-year-old girl showing distribution of lesions in cases of herpes necrotizing encephalitis diagnosed virologically. (Reprinted from the *British Medical Journal*, 1966, i, 1519, by permission of the Authors and Editor.)

Infection may be acquired at birth from virus in the mother's genital tract, or after birth from the mother or attendant with active recurrent herpes. Such cases may be found to have vesicular lesions on the skin or a conjunctivitis pointing to skin or eye as the portal of entry (Zuelzer & Stulberg, 1952). Virus probably reaches the CNS via the bloodstream. In a few cases of the fulminating disseminated type of herpes simplex in premature infants a history has been obtained of recurrent herpes in the mother (MacCallum, 1959). In such cases one would expect the mother to have maternal antibody and that this would cross the placenta and be present in the child's serum at birth. This antibody would be mainly IgG or 7S globulin; it is possible in order to limit infection acquired through a mucous surface, particularly if it is overwhelming, that specific antibody would be required in the secretory IgA fraction. IgA is a macroglobulin and does not normally cross the placenta.

It would appear from serological results that some of the cases of acute encephalitis in older children and adults have resulted from primary infection. Of eleven cases in adults five showed a marked increase in herpes CF antibody from undetectable levels within the first 7–10 days of the illness to titres usually encountered in primary herpetic infections. Three other cases without a history of recurrent herpes showed a rise in antibody of four-fold or greater, and three patients with a history of having recurrent herpes but not associated with the encephalitic illness also showed a rise in antibody of at least four-fold. It would seem, therefore, that the CNS may be involved as a result of either primary or recurrent infections. The routes by which virus spreads to the central nervous system are not known but presumably it can spread by haematogenous routes or nerve pathways such as along the olfactory nerves, or by both routes. Blood stream spread would appear unlikely in the presence of antibody in which case one must postulate spread via nerve pathways or by some other route. Whatever the mode of spread may be one cannot escape the conclusion that the extraordinary localization of lesions in herpes necrotizing encephalitis is to some extent the result of a predilection of herpesvirus for cells in the areas of the brain involved.

Diagnosis of herpetic encephalomyelitis

Aseptic meningitis caused by herpes simplex can only be distinguished from other viral causes such as mumps and Coxsackie viruses by appropriate virological procedures employing virus culture and antibody determinations. The recent development of anti-viral drugs, such as idoxuridine against herpes simplex and other DNA viruses makes the early diagnosis of herpetic necrotizing encephalitis of

special importance, as to be effective the drug must be used before neuronal necrosis is too far advanced. The problem of differential diagnosis of herpetic encephalitis from other space-occupying lesions has already been discussed in Part I (Campbell, 1969). Laboratory tests are now available which can assist in the early diagnosis of herpes encephalitis. These are aimed at rapid identification of viral antigen and virus isolation from cortical biopsies.

Examination of spinal fluid. In most cases reported the spinal fluid has been abnormal but it is important to remember that it may be normal. Pleocytosis of 50–300 cells/mm³ with predominantly mononuclear cells is not uncommon. The sugar level is usually normal and the protein may be raised to 70–150 mg/100 ml. These findings and absence of micro-organisms are useful in distinguishing viral from bacterial infection of the CNS. If the sugar level of the CSF is low or marginal a further specimen should be examined together with a blood sugar because of the importance of tuberculous meningitis in the differential diagnosis. The sugar level in herpes encephalitis is never consistently low and does not continue to fall as in untreated cases of tuberculous meningitis.

Demonstrating viral antigen. The presence of herpesvirus particles or antigen can be demonstrated by electron-microscopy and by fluorescence microscopy on cortical biopsy specimens. Both are of the greatest value and, provided the virologist is warned before the operation takes place so that the appropriate material can be collected, a precise diagnosis may be possible within a few hours of collecting the specimen. Harland *et al.* (1967) have reported six fatal cases in which virus particles were demonstrated in brain material and one further case treated with IDU.

Virus culture. Spinal fluid or biopsy material or both should be inoculated into susceptible cell cultures, for example human amnion, rabbit kidney or human fibroblasts. Specific cytopathic changes have been reported in a number of cases within 24 hr of inoculation (MacCallum, Potter & Edwards, 1964). The early appearance of lesions from these cases is probably a reflection of the amount of virus antigen present. This is borne out by the finding of virus particles in the biopsies because as a general rule the ease with which virus particles are found by electron-microscopy is related to the number present.

Serological tests for herpes antibody. These should be carried out whenever possible in order to obtain

more information about the pathogenesis of this type of infection. They are of limited diagnostic value. Sera should be collected as early as possible after the onset of neurological disease and again 10–14 days later and tested both by neutralization and complement-fixation because of some cross-antigenic relationship between the viruses of herpes simplex and varicella-zoster.

Herpesvirus simiae (B virus encephalomyelitis)

Herpesvirus simiae (B virus) is the simian variant of herpes simplex. The two viruses are closely related antigenically, but differ markedly in virulence.

Natural history

The natural history is very similar to that of herpes in man. Monkeys provide the reservoir. Primary infections occur mainly in young monkeys and are usually sub-clinical. Ten to 15% of newly-caught monkeys may have antibodies to B virus and the percentage may rise to 60% when animals are housed in communal cages (Hull & Nash, 1960). Clinical disease usually presents as a stomatitis with vesicles and ulcers on the tongue, lips and gum margins. The similarity of this condition to herpetic gingivostomatitis is striking.

Pathogenesis and epidemiology

Keeble, Christofinis & Wood (1958) found that 2.3% of monkeys had mouth lesions when examined on arrival in this country. The incidence of antibody to B virus was found to be 17% in normal monkeys used for poliovaccine production. The incidence is higher in rhesus monkeys but any species of monkey should be regarded as a potential carrier of the virus. The virus is present in large amounts in monkey saliva. In infected monkeys focal lesions with perivascular cuffing and glial infiltration in the roots of the fifth and seventh nerves can be found and also in the tractus solitarius.

Human infections

In the past 30 years fifteen cases of B virus infection have occurred and thirteen have been fatal (Perkins & Hartley, 1966). The majority have occurred in the past 10 years since the large-scale production of polio vaccine which entails the use of large numbers of experimental animals. Nearly all such infections have been associated with trauma, either a bite from a monkey or direct inoculation of infected material, saliva or tissue culture fluid into the skin. Infection can also be acquired via the respiratory tract. A local vesicular lesion may develop at the site of entry of the virus. In contrast to herpes simplex virus introduced by trauma, B virus spreads rapidly via lymphatics to regional lymph nodes and

then by the bloodstream to the CNS and other organs. In the CNS lesions may be found predominantly in the cord with intense necrosis of nerve cells. Extensive lesions may also be found as high as the medulla and brain-stem. Intranuclear inclusion may be difficult to find.

Prevention and treatment

B virus is a lethal disease in man. There is no specific treatment and there are limitations to the use of specific prophylactic procedures. The main emphasis should be placed on preventive measures and ensure that animal handlers and all scientific staff are aware of the risk and take precautions to see that the risk of infection is minimized. Instructions regarding this have been prepared by Perkins *et al.* (1966). If these are adhered to the risk of further cases should be materially reduced. In the event of a monkey bite immediate steps should be taken to treat the wound locally. The monkey should be carefully examined by trained staff for evidence of B virus infection.

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