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Herpes simplex virus infections

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INFECTION with herpes simplex virus is probably the commonest of all virus infections. The first attack occurs generally between the age of 1 and 5 years but may be deferred until adult life; it is usually sub-clinical or so trivial as not to justify medical attention but in 10% of cases it takes the form of *acute gingivo-stomatitis*. It is not sufficiently realized, however, that the virus may also be responsible for primary infection of the central nervous system, eye, skin and genital tract and that the eczematous skin is extremely vulnerable. Recurrent attacks of herpes simplex, usually taking the form of an eruption around the lips (herpes labialis) are common. These are due to reactivation of virus remaining latent in the cells of the buccal mucosa and around the mucocutaneous junction following the primary attack. A wide variety of factors predispose to reactivation including infections with organisms such as the pneumococcus or meningococcus, or by the common cold or influenza viruses, exposure to sun or cold, emotional upsets or hormonal disturbances such as menstruation.

The aetiological agent

Herpes simplex virus was successfully transmitted to the scarified cornea of the rabbit as long ago as 1912. It is also notable in that it was the first virus to be grown on the chorio-allantoic membrane of the chick embryo. It is a DNA virus with a diameter of 100–200 m μ and is readily transmitted to a variety of animals including rabbit, mouse, guinea-pig and hamster. In addition to chorio-allantoic membrane and rabbit cornea, the virus can be grown on HeLa cells and human amnion.

Pathology

The histological picture of an herpetic vesicle shows: (a) eosinophilic intranuclear inclusion bodies, (b) multinucleated giant cells, and (c) ballooning degeneration of the epithelial cells. Although the changes are similar, the lesions on the mucous membranes present as shallow ulcers and rarely as vesicles.

In the central nervous system, herpes simplex virus infection may produce extensive cerebral oedema and necrosis of brain tissue with cava-

tion resembling a necrotic abscess of bacterial origin but with little or no inflammatory capsule. Although lesions may occur in any part of the brain and be unilateral or bilateral, Haymaker *et al.* (1958) and other authorities report that the temporal lobe and thalamus are most frequently affected. In addition to the typical viral lesion of perivascular mononuclear cell infiltration Miller, Hesser & Tompkins (1966) describe three characteristic histological features, namely: (a) minute areas of ischaemic necrosis that tend to coalesce as infection progresses, (b) areas consisting of groups of well-formed erythrocytes ('lakes of blood') again with little surrounding reaction, and (c) basophilic degeneration of the nucleus of the neuron with distribution of the nuclear chromatin about the periphery. Later this central material becomes granular and finally shrinks into an eosinophilic mass surrounded by a clear halo. This cellular structure is the characteristic 'owl eye' of the Cowdry type A intranuclear inclusion of herpes simplex infection.

Clinical course

The incubation period of primary herpes simplex infection is probably about 4–5 days. In *acute herpetic gingivo-stomatitis* there is usually a sudden onset with high fever, intense irritability and a painful mouth due to the development of ulcers which present such a typical appearance as to be easy of diagnosis. They are characteristically shallow with a serpiginous edge and may be seen on any part of the buccal mucosa, tongue, gums or palate. The tissues are inflamed and bleed easily. Constitutional symptoms may be severe but usually subside in 5–7 days; local symptoms may persist for several weeks. Owing to the obvious difficulties involved in obtaining an adequate calorie intake and to the intense 'toxaemia' the general condition of the patient rapidly deteriorates and he becomes thin and emaciated. Routine electrocardiography generally reveals abnormalities indicating cardiac involvement.

Though less common, the primary attack may be in the *genital tract*, and while this generally occurs in the female, the male may also be infected. Initially single or multiple vesicles appear on the vulva but these spread to involve the vagina and cervix. After 2–8 days the vesicles rupture to become shallow ulcers with an erythematous, non-indurated base covered with membranous, greyish-yellow exudate. In primary infections, the ulcers are large, numerous and extensive associated with inguinal lymphadenopathy. Constitutional symptoms such as fever, headache, anorexia and epigastric pain lasting for 5–7 days, are associated with local symptoms such as dysuria, soreness of

the vulva and vagina, dyspareunia and sudden increase in vaginal discharge, which are more persistent. As in the case of herpes labialis, recurrent attacks may then be precipitated by trauma, menstruation, fever or emotional disturbance. In recurrent infections, the ulcers are much smaller and tend to be confined to one area. Constitutional symptoms do not usually accompany recurrent infections (Yen, Reagan & Rosenthal, 1965).

Neonatal infections occur in babies whose mothers do not possess herpes simplex antibody. The infection is acquired during passage through the infected birth canal and makes its appearance about 4–7 days after birth. The virus enters through skin, conjunctivae or mucous membranes and spreads by the blood stream to the liver, lungs, central nervous system and adrenal glands. Mortality is high.

Eczematous persons are particularly vulnerable to the viruses of herpes simplex and vaccinia both of which find in the affected skin an excellent pabulum for multiplication. Vesiculo-pustular lesions appear first on the erythematous areas and these may become generalized. The lesions of *eczema herpeticum* are smaller than those of *eczema vaccinatum* but the clinical evolution of the two conditions is otherwise similar. Not all cases have a favourable outcome.

Other skin lesions. Scattered skin lesions, pulpitis and paronychia, probably the result of auto-inoculation, may be the sole overt manifestation of infection with herpes simplex virus. The virus has been isolated from indolent skin ulcers in patients with malignant disease.

Central nervous system. Primary infection of the central nervous system with herpes simplex virus has until recently been considered rare. Herpetic meningo-encephalitis in infants was reported by Smith, Lenette & Reames (1941) and by Wildi (1951) and in adults by Zarofonetis *et al.* (1944) and by Whitman, Wall & Warren (1946). Ross & Stevenson (1961) described eight cases, six of which presented as meningo-encephalitis and two as encephalitis; they consider these forms more frequent than aseptic meningitis. When present, stomatitis preceded the development of encephalitis by several days. Although four of their cases made a rapid and apparently uneventful recovery, three showed residual neurological and psychological sequelae a year or more after the illness; the youngest died.

Although herpes simplex was often suspected of being the cause of acute encephalitis, diagnosis could only be based on post-mortem findings or serology. The possibility of much earlier diagnosis was indicated in a report by MacCallum, Potter &

Edwards (1964) from the Radcliffe Infirmary, Oxford. In two cases which presented with symptoms suggestive of cerebral abscess, herpes simplex virus was grown from material obtained by brain biopsy, confirming the diagnosis in 40 hr in one case and in 66 hr in the other. In neither case was there any external sign of infection with herpes simplex virus. In two further cases presenting with symptoms of cerebral abscess or tumour serological tests were consistent with recent infection with herpes simplex virus. This report clearly stimulated great interest in the subject and several subsequent reports indicate that the condition is much more frequent than was previously suspected.

It is generally agreed that, as suggested by Murray *et al.* (1966), the clinical course is divisible into two distinct stages, namely, a *prodromal irritative* stage lasting from a few days to a week in which the patients prove totally unresponsive to antibiotic therapy; this is followed by a stage characterized by evidence of *cerebral compression* and its sequelae. Miller *et al.* (1966) consider that suspicion 'should be aroused in any case presenting with headache and lethargy followed by confusion and stupor associated with evidence of cortical irritability'. Should the cerebrospinal fluid show xanthochromia or red cells or both, increased protein, and a predominantly mononuclear pleocytosis, there is a very high possibility of herpes encephalitis. Focal signs make the differential diagnosis from cerebral abscess difficult but in this event cerebral biopsy proves a most valuable diagnostic procedure. Miller and his colleagues were able to isolate virus from the cerebrum and pharyngeal secretions but not from the brain stem, spinal cord, cerebrospinal fluid or other viscera. In their twenty cases, diagnosis was confirmed either by isolation of the virus, detection of typical type A Cowdry intranuclear inclusions associated with perivascular mononuclear cell infiltration and areas of ischaemic necrosis, or by a rising titre of antibody. In three cases, Murray *et al.* (1966) found neither a history nor clinical evidence of herpetic lesions, but signs of meningeal involvement about 7-8 days, and limb paresis and terminal coma between 8 and 12 days, after the occurrence of the first symptoms. In all three cases there was a lymphocyte-polymorphonuclear pleocytosis associated with a slight rise in protein. Herpes simplex virus was isolated in both human amnion and monkey kidney from cerebral tissue in all three cases and mouse brain showed typical type A Cowdry intranuclear inclusions. Blackwood and his colleagues (1966) reporting a case of fatal necrotizing encephalitis in a 13-year-old girl also stress the difficulty that arises in the

diagnosis of patients who present with focal signs and raised intracranial pressure.

Treatment

There is no specific treatment. Painful lesions may be eased by the application of Gentian violet 1% but unfortunately this is an inelegant preparation which obscures the progress of the lesions. The cures that have been suggested for recurrent herpes are many and varied and include such empirical measures as Jennerian vaccination and simple psychotherapy. A vaccine consisting of sheep-embryo kidney cells and inactivated by ultraviolet light is reported to have given successful results (Lepine *et al.*, 1964). An anti-viral agent (5-iodo-2-deoxyuridine or I.D.U.) has given successful results in the treatment of herpetic iritis but was of no value in other forms of herpetic infection until Juel-Jensen & MacCallum (1965) showed that satisfactory results may be obtained if administered with the aid of a modified air-gun thus ensuring direct contact between the agent and the virus within the cell.

Eczematous children should be protected as far as possible from contact with adults with active herpetic lesions. Gentian violet 1% may be used in cases of eczema herpeticum. Gamma-globulin may have some value in protecting eczematous infants exposed to infection. In severe cases with a threat to life corticosteroids should be given early.

Since herpes simplex encephalitis is a progressive and highly destructive process, early diagnosis is essential if effective measures are to be taken. These include the administration of pooled gamma-globulin or selectively prepared human serum from patients with high antibody titres, and decompression with hypertonic solutions for cases with oedema of the brain. Caesarean section is indicated in patients with acute herpetic vulvovaginitis at or near term.

Summary

Infections with herpes simplex virus are among the commonest of all virus infections and their clinical manifestations are extremely protean. Whereas the majority of primary infections occur in the mouth, either the genital tract or central nervous system may be the site of attack. Herpetic meningo-encephalitis is much more frequent than has been hitherto realized, the condition is often progressive and there is a high mortality. Eczematous skins are particularly vulnerable to the virus, and the resultant eczema herpeticum may prove fatal. Other types of skin infection with herpes virus, particularly in patients with malignant disease, are by no means uncommon.

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