Epidemiology of herpes simplex keratitis

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Considerable information has been accumulated concerning the herpes virus and its relationship to man, its natural host (Table VI). It is evident that to control the diseases produced by the virus it is essential that some means be found not only to control the acute manifestations but also to eliminate the harbored virus from the readily available supply in the numerous ubiquitous carriers. Attempts to date to increase the natural human resistance against the virus have not been helpful.

The various factors and conditions that determine the frequencies and distributions of herpes simplex keratitis in the community have been reviewed by Scott in 1957. In the intervening years, a new approach to antiviral therapy has been introduced. Consideration of the epidemiology of herpes simplex keratitis may aid in the evaluation of this new group of antiviral compounds. It also may allow a forecast of the possible ways in which the new agent might be anticipated to influence the epidemiology of herpes simplex keratitis.

Herpes simplex infection is an endemic disease with approximately 90 per cent of the infections being subclinical. However, epidemics due to the herpes simplex virus have occurred. These have been reported in families in which more than one member has been affected either at the same time or in sequence from a common source, in hospital wards, and in institutions. The recorded epidemics caused by the herpes simplex virus have been of the stomatitis or eczematous variety and not ocular.6,7

Host parasite relationships

Herpes virus causes a high ratio of subclinical to clinical infections. Infected hosts remain carriers in the community without great disability to themselves. Man is the sole host. No other animal gets a natural infection from the virus. Other viruses of the herpes group, for example, the B virus and pseudorabies virus, do produce a natural infection in monkeys and hogs, respectively.

The herpes simplex virus is a highly adaptive one. It may live in latent form in man for many years causing little or no clinical evidence of disease. Thirty-three years ago it was well established by Andrews and Carmichael that a vast majority of normal adults have circulating antibodies against this virus and that the patients with frequent recurrences also have circulating antibodies.

The number of immunes in a population as measured by the presence of detectable humoral antibodies varies with age.

Recently, an analysis at Wills Hospital of 34 adult blood donors revealed that 90 per cent had positive neutralizing antibody titers. None had a history of herpes simplex infection of the skin, mouth, or eye.

This agrees with Buddingh and co-
workers, who found that over 90 per cent of adults had neutralizing antibody against herpes simplex. However, the findings could vary geographically as well as socially and chronologically. The percentage of immune newborn infants is the same as that of the adults, but decreases to a low level between the ages of 6 months and 2 years, thereafter increasing to that of the adult population by the age of 5 years. Dodd and co-workers as well as Burnet and Williams demonstrated that the herpes virus caused dermatitis in young infants who had no circulating antibodies and that, on recovery, they developed circulating antibodies.

Recognizable diseases caused by herpes simplex virus

The virus has the ability of involving the skin, the mucocutaneous junctions, mucous membranes, eyes, central nervous system, and genital areas (Table I). Although man is the natural host of the virus, it can be transmitted experimentally (Table II).

Recognition of carrier state

The carrier state can be recognized by isolation of virus and by antibody measurements. Antibody measurements include studies for neutralizing antibodies, complement fixation, and the skin test. The test for neutralizing antibodies is the most sensitive. It can be positive when the other tests are negative but the complement fixation test is less expensive and quicker. The latter is therefore widely employed for survey purposes. Scott has shown that there is a close correlation between the complement fixation test and the neutralizing antibody detection. In the population over 50 years of age there is a decrease in the incidence of the positive skin test despite the presence of complement fixation and neutralization antibodies. In infancy, the skin tests are unreliable. Skin tests appear to be of most value in older children and young adults. In these groups the skin tests have provided results comparable to those obtained by neutralization antibodies and complement fixation determinations.

Antibody titers, primary attack

The appearance of titers of virus neutralization antibodies rises steeply between the fourth and eighth days after a primary attack. Apparently it remains at a plateau for approximately 18 days. Following the primary attack, the antibody titer remains high for varying periods of 4 to 12 months. In some individuals it is barely detectable after 16 months, and in others it has disappeared in 5 to 8 months. The data suggest that, in the child, a single primary infection may not allow the parasite to establish itself but that repeated subclinical infections may have to occur until the balance is achieved and the host maintains a constant level of antibody.

Table I. Clinical manifestations of herpes simplex virus

<table>
<thead>
<tr>
<th>Eye</th>
<th>Epithelial</th>
<th>Stromal, nonulcerative</th>
<th>Stromal, ulcerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis, keratoconjunctivitis, keratitis, keratoconjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Herpes simplex, eczema herpeticum, traumatic herpes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Herpes labialis, acute herpetic gingivostomatitis, recurrent stomatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose</td>
<td>Acute herpetic rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital</td>
<td>Vulvovaginitis, herpes progestitale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Meningoencephalitis associated with trigeminal neuralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated herpes</td>
<td>Neonates and adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Experimental infection with herpes simplex virus

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Guinea pig</th>
<th>Hamster</th>
<th>Cotton rat</th>
<th>Mouse</th>
<th>Embryonated hen's egg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue culture, variety of cells, e.g., Rabbit kidney</td>
<td>HeLa</td>
<td>Human amnion</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Table III. Decade distribution of herpes simplex keratitis

<table>
<thead>
<tr>
<th>Decade</th>
<th>No. of eyes</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (0 to 9)</td>
<td>182</td>
<td>8.3</td>
</tr>
<tr>
<td>2nd (10 to 19)</td>
<td>161</td>
<td>7.3</td>
</tr>
<tr>
<td>3rd (20 to 29)</td>
<td>202</td>
<td>9.1</td>
</tr>
<tr>
<td>4th (30 to 39)</td>
<td>306</td>
<td>13.9</td>
</tr>
<tr>
<td>5th (40 to 49)</td>
<td>433</td>
<td>19.7</td>
</tr>
<tr>
<td>6th (50 to 59)</td>
<td>399</td>
<td>18.2</td>
</tr>
<tr>
<td>7th (60 to 69)</td>
<td>306</td>
<td>13.9</td>
</tr>
<tr>
<td>8th (70 to 79)</td>
<td>146</td>
<td>6.6</td>
</tr>
<tr>
<td>9th (80 to 89)</td>
<td>53</td>
<td>2.4</td>
</tr>
<tr>
<td>10th (90 to 99)</td>
<td>1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

\[= 65.7\%\]

Table IV. Occurrence of herpes simplex keratitis

<table>
<thead>
<tr>
<th>First ocular manifestation</th>
<th>Recurrent ocular involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,164</td>
<td>1,081</td>
</tr>
</tbody>
</table>

Recurrent attack

Usually no alteration in antibody titers occurs with recurrent manifest attacks but some adults react to recurrent attacks by a rise in antibodies, either neutralizing, complement fixing, or both.

Determinations of susceptibles

The greatest incidence of susceptibility appears to lie between 6 and 24 months of age. Subclinical attacks are greater than clinical. Therefore absence of a history of a primary illness is not of great value in determining the incidence of susceptibility. This must be done by measuring the presence of antibodies in the population at large.

Socioeconomic and environmental conditions

The incidence of infection is considerably higher among persons in the lower socioeconomic bracket than those in the higher. The amount of overcrowding and the level of public health education appear to increase and decrease, respectively, the incidence in a given population.

Table V. Sex distribution of herpes simplex keratitis

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td>1,378 (61%)</td>
<td>886 (39%)</td>
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Occurrence of ocular involvement

As a result of the recent attempts to evaluate IDU in the therapy of herpes simplex keratitis, a large number of ocular cases have been recorded. The statistics of the series observed at the Wills Hospital by Dr. Peter Laibson and myself have been combined with those obtained from Smith Kline and French Laboratories through the courtesy of Thomas Gower, and those provided by Alcon Laboratories, Inc., through the courtesy of Drs. Carl Aijan and Earl Maxwell. These are recorded in Tables III, IV, and V. Each series showed a remarkable similarity in distribution.

The youngest subject in the series was 6 weeks of age. There were only 3 in the first year of life. It is obvious that no decade is free of ocular involvement, and that the greatest number of cases occurred in the fourth to seventh decades. These years accounted for two thirds of all the patients. Males predominated in all series. Recurrent cases constituted almost 50 per cent (48.5 per cent) of the analyzed eyes.

Incubation period

Evidence from various sources suggests a range between 2 and 12 days for incubation of the herpes infection with a peak at 4 days. A recent analysis by Hale and associates suggested a mean incubation period in children of 6.8 days, which is within the range calculated by earlier workers.

Epidemics

This is essentially an endemic disease. Approximately 90 per cent of the infections are subclinical. However, there are epidemics of herpes simplex infections of the mouth and skin. These usually require special prerequisites: families exposed to...
the same source and hospital wards where those with skin lesions such as eczema can be exposed to a fresh case. This is particularly true in institutions.

Mechanism of spread

Overcrowding and close body contact which frequently occurs in infancy predispose to the infection. In adults, kissing and sexual intercourse have been demonstrated to be prime methods of spreading the disease. The higher incidence and crowded conditions of the lower socioeconomic groups support the likelihood of spread by direct contact.

Trauma appears to act as a trigger mechanism making it possible for a subclinical infection to become a clinical one. Foreign body injuries of the cornea, intraocular surgery, and general anesthesia have occasionally precipitated keratitis. Scott noted that gum massage and teething can precede the onset of stomatitis.

Recurrent herpes

The ophthalmologic literature has called attention to the predisposing nature of overexposure to sunlight, wind, anesthesia, and foreign bodies in recurrent attacks of herpes. This is also true of labial herpes. Fever due to infections or artificially induced has triggered corneal and labial herpes. There appears to be a correlation between the menses and onsets of attacks. Carton and Kilburne have pointed out that sections of the trigeminal sensory route are frequently followed by herpetic lesions on that side. Blank and Brody have noted a personality pattern of people with recurrent attacks. They feel that these individuals were submissive, sweet and good, emotionally immature, and dependent. With arousal of their resentment, herpes followed. Others have pointed out that feelings of hostility were frequently followed by recurrent attacks.

Steroids are definitely a triggering agent, in some patients, whether they are given locally or systemically. The basic stimulus for the appearance of a recurrent lesion is not a reinfection from without but a disturbance in the physiology of the host which activates a latent virus.

Latent state of virus

Latency of virus in human infections with herpes simplex has long been a perplexing phenomenon. It is an accepted principle of recurrent infections whether they involve herpetic stomatitis, dermatitis, or keratitis, yet it depends for the most part upon indirect evidence. Although virus persistence in recovered tissues has, up till now, not been observed to occur naturally in animals, recent studies have shown that latency and recurrence can be demonstrated experimentally in mice and rabbits. Schmidt and Rasmussen showed that 60 per cent of the mice that had recovered from herpes, administered intracerebrally, had spontaneous encephalitis and died when given 0.5 to 2 mg. of adrenalin intramuscularly. Glutathione, cortisone acetate, and a bacterial pyrogen were other drugs tested in similar fashion but were found to have no effect.

Good and Campbell were able to obtain an experimental herpetic encephalitis in rabbits by initiating a nonspecific
anaphylactic shock. Later, Anderson, Margruder, and Kilbourne\(^7\) were able to reactivate and isolate herpes virus from previously infected and healed rabbit corneas. Their method of stimulating such corneas was to sensitize the animals with horse serum and then induce an Arthus reaction in the healed cornea. They were able to isolate virus from eyes 7 times following 19 attempts at induction.

A new and novel hypothesis has been suggested by Herriot\(^10\) to account for the phenomenon of recurrent herpes infections in many persons in spite of a high level of circulating serum neutralizing antibodies. It is suggested that the virus may be present as free desoxyribonucleic acid (i.e., incomplete virus lacking its outer protein shell), and as such be serologically unreactive but still infective. He postulates that the in-between episodes of noninfectivity may be due to the presence of humoral nucleases, and cites evidence that white blood cells, which can release desoxyribonuclease inhibitor in vitro, increase in number during fever. Thus, the recurrence of a herpetic lesion would be possible under conditions of stress, and latency would, under this system, really be an expression of viral survival as a free nucleic acid.

Reservoir of infection

Subclinically infected carriers provide the bulk of the group harboring the virus. It should be noted that patients with stomatitis may excrete virus in their saliva intermittently for as long as 7 weeks. The stools also can harbor the virus. It appears several days after first detection in the saliva. The eye may have the virus in the absence of clinical signs of infections, but it is a less likely source of spread of the disease than the oral area. The virus has been recovered from 2.5 per cent of the saliva of asymptomatic adults.

Control measures

At the present time we have no specific control measures. However, it would be essential in patients who have recurrences that the recognized precipitating factors be avoided, such as overexposure to ultraviolet rays and avoidance of the emotional upsets which can precede a recurrence. Perhaps in those who have frequent attacks with menstruation, fever, and trauma, an agent such as IDU or a superior compound to be developed in the future might be instilled as a prophylactic measure during these stress periods. Perhaps this will alter the number of recurrent attacks. There is evidence that the use of IDU, when steroids are required, may reduce the severity and perhaps the frequency with which recurrent herpetic keratitis develops in the epithelium. Vaccination with herpes virus either dead or alive would appear to be, on the basis of our present knowledge, unsound. It has been shown to be hazardous if live virus is used.\(^{14,15}\)

REFERENCES


