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Herpes simplex virus type 1 and respiratory disease in critically-ill patients: real pathogen or innocent bystander?

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ABSTRACT

Herpes simplex virus type 1 (HSV-1) has been associated with pulmonary disease, mostly in severely immunocompromised patients. After reactivation and shedding in the oropharynx, the virus may reach the lower respiratory tract by aspiration or by contiguous spread. HSV-1 can be detected in clinical specimens by virus culture or quantitatively by nucleic acid amplification techniques. With these techniques, HSV-1 is often detected in the respiratory secretions of critically-ill patients. However, a clear diagnosis of HSV-1 pneumonia is difficult to establish because clinical criteria, radiological features and laboratory findings all lack specificity. Lower respiratory tract HSV-1 infections have not been associated with specific risk-factors. There is also an absence of consistent data concerning the effect of antiviral treatment on the outcome of critically-ill patients. Further studies are needed to better define the pathogenic role of HSV-1 in the lower respiratory tract of these patients, to improve the diagnosis, and, especially, to assess the need for antiviral treatment in the individual patient.

Keywords Critically-ill patients, diagnosis, herpes simplex virus, pathogenesis, respiratory tract infection, review

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INTRODUCTION

Herpes simplex virus type 1 (HSV-1) causes a variety of infections that involve mucocutaneous surfaces, the central nervous system and, occasionally, visceral organs such as the lung [1,2]. The virus has been reported to be associated with pulmonary disease since 1949 [3], but until two decades ago, HSV pneumonia was considered to be rare. This diagnosis was usually based on autopsy findings [4–11]. The more frequent use of fibreoptic bronchoscopy and bronchoalveolar lavage (BAL) in recent years has resulted in the virus being isolated with increasing frequency from respiratory secretions. This has been paralleled by an increase in the frequency of the diagnosis of HSV tracheobronchitis or pneumonia, mostly in immunocompromised hosts [12–19]. However, the significance of the presence of HSV-1 in respiratory secretions from these patients, and especially from mechanically-ventilated patients, is still a topic for debate. This review focuses on the potential clinical importance of HSV-1 respiratory infections in critically-ill patients, with special reference to the controversies in the literature concerning pathogenesis, clinical spectrum, risk-factors and response to antiviral therapy.

THE CAUSATIVE AGENT

HSV-1 can infect nearly every mucocutaneous and visceral site in the human body. Infections with HSV in humans have been described since ancient Greek times [20,21]. The word *herpes*, which means to creep or to crawl, is found in the original Greek description of the appearance of spreading skin lesions [22]. Clinical descriptions

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of herpes labialis go back to the time of Hippocrates [21]. Early in the 20th century, the virus was transmitted successfully from humans to various animals. The virus was cultured in rabbit testicular tissue as early as 1925, isolated in chick embryos in 1940, and grown successfully in conventional tissue culture systems about 15 years later [21]. The histological association of herpes virus infection with the formation of multinucleated giant cells with intra-nuclear inclusions was first described in 1934 [23].

HSV-1 is classified in the α-herpes virus group of the Herpesviridae, together with HSV type 2 (HSV-2) and varicella-zoster virus. All herpes viruses possess an internal core with a single large, linear, double-stranded DNA molecule, an icosahedral capsid with 162 capsomeres, and a lipid envelope. HSV-1 encodes at least 80 different structural and non-structural polypeptides, including ten different glycosylated proteins. The predominant antibody response to HSV infection is raised against these surface glycoproteins. There is extensive cross-reactivity among the different glycoproteins of HSV-1 and HSV-2. Therefore, differentiation between HSV-1 and HSV-2 infections in commercial antibody assays is not possible. Type-specific antibody assays based on glycoprotein G1 (gG1) for HSV-1 and glycoprotein G2 (gG2) for HSV-2 exist, but are used rarely in routine diagnostic laboratories. The virus structure, function and biological properties have been extensively described previously [2,24–26].

PATHOGENESIS

HSV infections are very common in the human population. Primary HSV infections are usually asymptomatic, but can manifest as gingivostomatitis or pharyngitis [1,2]. Following initial acquisition, HSV-1 establishes latency and remains in a non-replicating form in sensory ganglia for life, commonly in the trigeminal ganglia, but the virus has also been isolated from the superior cervical and vagus ganglia [27,28].

Depending on age (> 5 years) and socio-economic status, 40–98% of the human population in different countries has antibodies to HSV-1 [29–32]. Despite the presence of these antibodies, the virus reactivates intermittently, following local stimuli (e.g., tissue lesion or UV light) or systemic stimuli (e.g., fever, hormonal imbalance or impairment of the immune system during emotional stress or surgery). Reactivation of HSV-1 has been associated with asymptomatic virus excretion in saliva [33–36], ulceration of the mouth mucosa or herpes labialis [37–40], or more serious disease such as herpetic oesophagitis [10,41,42], tracheobronchitis or pneumonia in immunocompromised hosts [4,11,12,14,16,17,19,36,43–48]. Because the primary infection is often asymptomatic, reactivation can be the first clinical manifestation of infection.

Classically, HSV-1 infects squamous epithelium [4,36]. Factors promoting squamous metaplasia, such as trauma, smoking, burns, radiation therapy or chemotherapy, are mentioned in several studies as predisposing the patient to lower respiratory tract infection by HSV [36,46,49]. However, metaplasia may also occur as a secondary response to the infection itself, as the virus is known to cause cytotoxic changes in the respiratory mucosa, with disruption of the protective mucociliary surface [12]. It has also been suggested that intubation, instrumentation and mechanical trauma of the airways predispose to herpetic pulmonary infections [5,6,9,45]. Airway trauma is likely to make the trachea more susceptible to infection with HSV by permitting the virus to migrate from the oral cavity to the trachea by contiguous spread [11]. However, not all patients from whom HSV-1 is isolated from the lower respiratory tract are intubated [12,36,43].

HSV-1 may reach the lower respiratory tract by three different routes. Contiguous spread to the lung parenchyma, or aspiration of the virus in patients shedding the virus from mucocutaneous or oropharyngeal lesions, may play a role in many cases [6]. Focal necrotising pneumonitis has been suggested to result from this local spread [11,50]. Dislodgement of infected particles from the mucous adhesive layer inside the endotracheal tube, followed by their migration to the lower airways, may also contribute to this mechanism [51]. The concept of haematogenous seeding is supported by Ramsey *et al*. [11], and is thought to lead to diffuse interstitial pneumonia. Recovery of HSV from circulating lymphocytes or peripheral buffy coat blood cells provides support for this hypothesis [36,52]. A third mechanism, namely reactivation of latent infection within the vagal ganglion, with spread along the vagus nerve to the lung epithelium, has also been postulated [43]. This suggestion is supported by the isolation of