Commentary

Think outside the box: extrapulmonary manifestations of severe respiratory syncytial virus infection

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Published: 24 August 2006
This article is online at http://ccforum.com/content/10/4/159

Critical Care 2006, **10:**159 (doi:10.1186/cc5012)

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Abstract

Extrapulmonary effects of severe respiratory syncytial virus (RSV) infection are not uncommon. Dr Eisenhut's systematic review of extrapulmonary manifestations of severe RSV infection clearly demonstrates clinical consequences peripheral to the lung parenchyma. The extrapulmonary impact of RSV infection raises questions as to whether these are direct RSV effects (i.e., RSV infection of site-specific tissue), secondary to parenchymal lung disease and its causative respiratory failure, or the result of inflammatory mediators dispersed from the provoked respiratory epithelium.

> "Oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful."
>
> Reynolds and Cook (1963) [1]

Respiratory syncytial virus (RSV) was first identified in 1956 as the agent that causes chimpanzee coryza and subsequently isolated from children in 1957. Since then this medium-sized enveloped RNA paramyxovirus has been recognised as the single most important virus causing acute respiratory tract infections in children. The virus replicates in nasopharyngeal epithelium and then spreads to lower respiratory tract one to three days later. RSV infects respiratory epithelial cells by attaching itself to the cell surface by means of an envelope glycoprotein, the G (attachment) protein. A second envelope glycoprotein, the F (fusion) protein, mediates fusion with the epithelial cell membrane along with adjacent cells, resulting in the formation of multinucleated cells – syncytia – for which the virus is named.

The vast majority of RSV research and studies have concentrated on the lungs and the mechanics of pulmonary immunopathology. Dr Eisenhut's thorough systematic review of extrapulmonary manifestations of severe RSV infection [2] clearly demonstrates clinical consequences peripheral to the lung parenchyma. It begs the question as to whether these are direct RSV effects (i.e., RSV infection of that tissue) or indirect, being secondary to parenchymal lung disease and its causative respiratory compromise or consequential of prowling inflammatory mediators?

RSV, like the other *Paramyxiviridae*, can infect non-epithelial cells if it can gain access to the receptors on their surface, as demonstrated by the use of monkey kidney cells for RSV culture *in vitro*. The transit of RSV to distant organs would have to be haematogenous. RSV-RNA has been detected by RT-PCR in whole blood but not plasma of infants and neonates [3,4], but this alone merely indicates cell-associated RSV genome. This is not necessarily viable RSV and is likely to be virus phagocytozed by neutrophils or monocytes. To escape their white cell captors RSV would need to replicate and break out, which has not yet been demonstrated. Viable RSV floating freely in plasma would hold the potential for distant RSV infection.

Evidence of deposition in distant organs comes from detection in the myocardium [5,6], liver [7], and cerebrospinal fluid [8]. However, strong convincing evidence of RSV-related inflammation or infection of these sites is less forthcoming. Elevated cardiac troponin levels in infants with severe RSV infection are well described [9,10]. Unfortunately, this is not necessarily indicative of RSV-directed myocardial injury, but more likely the result of (right) heart strain secondary to severe lung parenchymal disease [10]. Likewise, it is highly suggestive that raised hepatic transaminases in this patient group are consequential to hepatic congestion or ischaemia due to right heart failure,

IFN = interferon; IL = interleukin; RSV = respiratory syncytial virus.

itself secondary to parenchymal lung disease and/or pulmonary hypertension [11]. Proof of a RSV hepatitis would take histological verification (i.e., liver biopsy), which for ethical reasons is only ever going to occur postmortem. Apnoeas and seizures undoubtedly occur in RSV infection, but presently there is more support for RSV encephalopathy than RSV encephalitis [12-15]. Unfortunately, many of the reports fail to adequately adjust for the confounding consequence that hypoxic episodes and hypercapnoea may have on the patient's neurological status. When not related to hypoxic or electrolyte imbalance triggers, RSV's central influence/effect is probably related to released neurotoxic inflammatory chemokines and cytokines [12,16,17]. Endocrine impact/consequences, although interesting, appear to be the sequelae of severe RSV pulmonary disease and/or its treatment. It is likely that occurrences of hyponatraemia and hyponatraemic seizures are largely related to the use of hypotonic/electrolyte-poor intravenous solutions [18]. Further research is required to scrutinize whether the reported neuroendocrine stress response in RSV bronchiolitis is no more than an epiphenomenon reflecting severity of RSV disease [19].

Most of the extrapulmonary effects are likely to be the end result of released inflammatory mediators such as cytokines and chemokines triggered by the RSV respiratory tract infection. The antiviral and cell-mediated immune reaction to RSV infection is primarily orchestrated by RSV-infected respiratory epithelial cells and by alveolar macrophages. The storm of T helper 1-type cytokines (IFNγ, IL-2, IL-12), T helper 2-type cytokines (IL-4, IL-5, IL-6, IL-10), antiviral interferons (IFNα, IFNβ) and chemokines (C, CC, CXC and CX_3C subgroups) released from respiratory epithelial cells may regulate the immune profile and reaction in outlying cells [16,17,20]. Host genetic factors may further manipulate the immune-augmented response at distant extrapulmonary sites.

Extrapulmonary effects of severe RSV infection are not uncommon. Dr Eisenhut [2] is correct to remind clinicians of them so that they may be vigilant to their occurrence and consequences. The challenge for researchers is to discern whether these extrapulmonary effects are as a result of site-specific RSV infection or inflammatory mediators dispersed from the provoked respiratory tract. Although the basic sentiments of Reynolds and Cook [1] still ring true, the understanding of RSV disease and its treatment options has progressed over time.

Competing interests

The authors declare that they have no competing interests.

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