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 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,
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 CX3C 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.

References
1. Reynolds EOR, Cook CD: The treatment of bronchiolitis. J Pediatr 1963, 63:1205-1207.
2. Eisenhut M: Extrapulmonary manifestations of severe respiratory syncytial virus infection – a systematic review. Crit Care 2006, 10:R107.
3. O’Donnell DR, McGarvey MJ, Tully JM, Balfour-Lynn IM, Openshaw PJ: Respiratory syncytial virus RNA in cells from the peripheral blood during acute infection. J Pediatr 1998, 133:272-274.
4. Rohwedder A, Keminer O, Forster J, Schneider K, Schneider E, Werchau H: Detection of respiratory syncytial virus RNA in blood of neonates by polymerase chain reaction. J Med Virol 1998, 54:320-327.
5. Bowles NE, Ni J, Keamey DL, Pauschinger M, Schultheiss HP, McCarthy R, Hare J, Bricker JT, Bowles KR, Towbin JA: Detection of viruses in myocardial tissues by polymerase chain reaction. Evidence of adenovirus as a common cause of myocarditis in children and adults. J Am Coll Cardiol 2003, 42:467-472.
6. Fishaut M, Tubergen D, McIntosh K: Cellular response to respiratory viruses with particular reference to children with disorders of cell-mediated immunity. J Pediatr 1980, 96:179-186.
7. Nadal D, Wunderli W, Meermann O, Briner J, Hirsig J: Isolation of respiratory syncytial virus from liver tissue and extrahepatic biliary atresia material. Scand J Infect Dis 1990, 22:91-93.
8. Zlateva KT, Van Ranst MV: Detection of subgroup B respiratory syncytial virus in the cerebrospinal fluid of a patient with respiratory syncytial virus pneumonia. Pediatr Infect Dis J 2004, 23:1065-1068.
9. Checchia PA, Appel HJ, Kahn S, Smith FA, Shulman ST, Pahl E, Baden HP: Myocardial injury in children with respiratory syncytial virus infection. Pediatr Crit Care Med 2000, 1:146-150.
10. Eisenhut M, Sidaras D, Johnson R, Newland P, Thorburn K: Cardiac troponin T levels and myocardial involvement in children with severe respiratory syncytial virus lung disease. Acta Paediatr 2004, 93:887-890.
11. Eisenhut M, Thorburn K, Ahmed T: Transaminase levels in ventilated children with respiratory syncytial virus bronchiolitis. Intensive Care Med 2004, 30:931-934.
12. Kho N, Kerrigan JF, Tong T, Browne R, Knilans J: Respiratory syncytial virus infection and neurologic abnormalities: Retrospective cohort study. J Child Neurol 2004, 19:859-864.
13. Sweetman LL, Ng Y-T, Butler IJ, Bodensteiner JB: Neurologic complications associated with respiratory syncytial virus. Pediatr Neurol 2005, 32:307-310.
14. Ng Y-T, Cox C, Atkins J, Butler IJ: Encephalopathy associated with respiratory syncytial virus bronchiolitis. J Child Neurol 2001, 16:105-108.
15. Lindgren C, Groegaard J: Reflex apnoea response and inflammatory mediators in infants with respiratory tract infection. Acta Paediatr 1996, 85:798-803.
16. Openshaw PJM: Antiviral immune responses and lung inflammation after respiratory syncytial virus infection. Proc Am Thorac Soc 2005, 2:121-125.
17. Tripp RA, Oshansky C, Alvarez R: Cytokines and respiratory syncytial virus infection. Proc Am Thorac Soc 2005, 2:147-149.
18. Hanna S, Tibby SM, Durward A, Murdoch IA: Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr 2003, 92:430-434.
19. Tasker RC, Roe MF, Bloxham DM, White DK, Ross-Russell RI, O’Donnell DR: The neuroendocrine stress response and severity of acute respiratory syncytial virus bronchiolitis in infancy. Intensive Care Med 2004, 30:2257-2262.
20. Culliford PJ, Pennycook AM, Tregown JS, Russell T, Openshaw PJ: Differential chemokines expression following respiratory syncytial virus infection reflects Th1- or Th2-biased immunopathology. J Virol 2006, 80:4521-4527.