

Leading article

Measles virus and Crohn's disease: view of a medical virologist

Some recent reports have claimed that persistent measles virus infection is involved in the aetiology or pathogenesis, or both, of Crohn's disease. Using a variety of techniques, such as direct electron microscopy, immunohistochemistry and in situ hybridisation, these authors report that measles virus particles, protein or RNA were detected in tissues from patients with Crohn's disease.¹⁻⁵ These observations led to the hypothesis that exposure to measles virus early in life, either during pregnancy, or as a consequence of post-natal infection by wild type measles virus or measles vaccination, predisposes to inflammatory bowel disease (IBD).^{6,7} These claims prompted publication of several critical commentaries and responses and led to a case control study which did not support an association between measles virus vaccination and IBD.⁸⁻¹⁹ The comments focused on the possible short-comings of the methods used by the researchers as well as the choice of control cohorts with respect to their exposure to the infectious agent and their incidence of IBD. Thus, for example, in many virus-host systems, it has been shown that diagnosis based on morphology can be misleading as viral structures may resemble normal cellular elements. Similarly, immunogold staining of viral structures, immunohistochemical detection of viral proteins and the in situ hybridisation of viral nucleic acids in tissue sections are all methods that are subject to problems of specificity, particularly when used at high sensitivities. In such cases, polymerase chain reaction (PCR) technology combined with sequencing of the amplified nucleic acid is the most reliable approach to obtain clear cut data. However, the PCR technique has failed to detect measles virus transcripts in diseased tissue of patients with Crohn's disease.^{20,21}

In addition, the data relating to the humoral immune reactions against measles virus in patients with Crohn's disease are controversial. Whereas one group found measles virus specific IgM antibodies in the majority of patients, others could not detect any immunological evidence of persistence of measles virus or any differences compared with control groups.²²⁻²⁴ If the latter observation is correct, it would not support the view of a persistent measles virus infection, but rather an immune reaction in the course of an acute infection. Thus, the observations relating to a possible association of measles virus with Crohn's disease are very controversial and at present, there is no unequivocal evidence to support this hypothesis.

The discussions about the involvement of measles virus in Crohn's disease are reminiscent of those taking place for other diseases, such as multiple sclerosis, Paget's disease, otosclerosis, and various autoimmune disorders. As summarised in table 1, only acute measles with its various complications, measles inclusion body encephalitis

Table 1 Human diseases associated with measles virus infection

Confirmed association	Suggested association
Acute measles	Multiple sclerosis
Complications of acute measles	Otosclerosis
Measles inclusion body encephalitis	Paget's disease
Subacute sclerosing panencephalitis	Various autoimmune disorders

(MIBE) and subacute sclerosing panencephalitis (SSPE), can be directly attributed to this morbillivirus infection at the present time. In each of these diseases, measles virus can always be detected using a variety of laboratory tests, and humoral and cell mediated immune reactions against this agent correlate with disease progression. Evidence of measles virus infection in the other diseases listed in table 1 is circumstantial. In multiple sclerosis, the major support for a possible viral aetiology derives from epidemiological studies implicating environmental factors encountered years prior to the onset of disease. Serological studies have revealed slightly higher or normal titres of measles virus antibodies in patients with multiple sclerosis compared with controls. In addition, measles virus specific RNA has been detected occasionally in scattered cells in brain tissue, but this is also true of controls. Other groups have failed to detect any measles virus RNA in brain tissue of patients with multiple sclerosis.²⁵ The only reasonable conclusion from these studies is that measles virus can persist in human brain, but that it is not necessarily aetiologically linked to multiple sclerosis. Similar virological and immunological findings have been observed for other viral agents—for example, herpes simplex virus, cytomegalovirus, and human herpes virus type 6 have been reported in patients with multiple sclerosis.²⁵ It is noteworthy that listeria, *Escherichia coli*, streptococcus, and human herpes viruses have been found and proposed as causal factors in IBD.^{26,27}

From a virological point of view, the incrimination of measles virus in the aetiology and pathogenesis of a human disease requires both the detection of measles virus and a virus specific immune response that correlates with the disease process. The detection of measles virus depends on the stage of virus-cell interaction. In an acute measles virus infection, virus can be isolated from different organ tissues quite easily. In persistent infections, such as MIBE or SSPE, isolation of infectious virus from brain tissue is the exception rather than the rule. However, viral proteins and viral nucleic acids are always detectable in brain tissue of patients with these two diseases by a variety of methods.²⁸ Moreover, as measles virus proteins are highly immunogenic specific humoral and/or cell mediated immune reactions are found in both acute and persistent virus

infections. In Crohn's disease, as with multiple sclerosis, the detection of measles virus in diseased tissue is not reproducible, maybe as a result of a low copy number of viral genes in infected cells. In such a situation, sequence determination is needed to confirm the presence of measles virus in diseased tissue. This has still to be achieved in IBD. Although Koch's postulates cannot always be fulfilled in subacute or chronic inflammatory disorders, attempts to link a conventional virus to such diseases requires both the detection of the agent and virus specific immune reactions in each and every case. It will be of interest to see whether this can be achieved in Crohn's disease.

V TER MEULEN

*Institut für Virologie und Immunbiologie,
Universität Würzburg,
Versbacher Strasse 7,
D-97078 Würzburg, Germany*

- 1 Wakefield AJ, Pittilo RM, Sim R, *et al.* Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993;**39**:345–53.
- 2 Miyamoto H, Tanaka T, Kitamoto N, *et al.* Detection of immunoreactive antigen, with a monoclonal antibody to measles virus, in tissue from a patient with Crohn's disease. *J Gastroenterol* 1995;**30**:28–33.
- 3 Wakefield AJ, Sim R, Akbar AN, *et al.* In situ immune responses in Crohn's disease: a comparison with acute and persistent measles virus infection. *J Med Virol* 1997;**51**:90–100.
- 4 Daszak P, Purcell M, Lewin J, *et al.* Detection and comparative analysis of persistent measles virus infection in Crohn's disease by immunogold electron microscopy. *J Clin Pathol* 1997;**50**:299–304.
- 5 Lewin J, Dhillon AP, Sim R, *et al.* Persistent measles virus infection of the intestine: confirmation by immunogold electron microscopy. *Gut* 1995;**36**:564–9.
- 6 Ekbohm A, Wakefield AJ, Zack M, *et al.* Perinatal measles infection and subsequent Crohn's disease. *Lancet* 1994;**344**:508–10.
- 7 Thompson NP, Montgomery SM, Pounder RE, *et al.* Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995;**345**:1071–4.
- 8 Patriarca PA, Beeler JA. Measles vaccination and inflammatory bowel disease. *Lancet* 1995;**345**:1062–3.
- 9 Farrington P, Miller E. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1362.
- 10 Hermon-Taylor J, Ford J, Sumar N, *et al.* Measles and Crohn's disease [letter]. *Lancet* 1995;**345**:922–3.
- 11 Thompson NP, Montgomery SM, Pounder RE, *et al.* Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1364.
- 12 Minor P. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1362–3.
- 13 MacDonald TT. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1363.
- 14 Calman KC. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1362.
- 15 Jones P, Fine P, Piracha S. Crohn's disease and measles [letter]. *Lancet* 1997;**349**:473.
- 16 Miller D, Renton A. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1363.
- 17 Baxter T, Radford J. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. *Lancet* 1995;**345**:1363.
- 18 Lione A, Scialli AR. Perinatal exposure to measles virus and the risk of inflammatory bowel disease. *Toxicology* 1997;**11**:647–52.
- 19 Feeney M, Clegg A, Winwood P, *et al.* A case-control study of measles vaccination and inflammatory bowel disease. *Lancet* 1997;**350**:764–6.
- 20 Iizuka M, Nakagomi O, Chiba M, *et al.* Absence of measles virus in Crohn's disease [letter]. *Lancet* 1995;**345**:199.
- 21 Haga Y, Funakoshi O, Kuroe K, *et al.* Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. *Gut* 1996;**38**:211–15.
- 22 Balzola FA, Castellino F, Colombaro P, *et al.* IgM antibody against measles virus in patients with inflammatory bowel disease: a marker of virus-related disease? *Eur J Gastroenterol Hepatol* 1997;**9**:661–3.
- 23 Touze I, Dubucquoi S, Cortot A, *et al.* IgM-specific measles-virus antibody in families with a high frequency of Crohn's disease. *Lancet* 1995;**346**:967–8.
- 24 Fisher NC, Yee L, Nightingale P, *et al.* Measles virus serology in Crohn's disease. *Gut* 1997;**41**:66–9.
- 25 ter Meulen V, Katz M. The proposed viral etiology of multiple sclerosis and related demyelinating diseases. In: Raine CS, McFarland HF, Tourtellotte WW, eds. *Multiple sclerosis: clinical and pathogenetic basis*. London: Chapman and Hall Medical, 1997:287–306.
- 26 Liu Y, van Kruininen HJ, West AB, *et al.* Immunocytochemical evidence of Listeria, Escherichia coli and Streptococcus antigens in Crohn's disease. *Gastroenterology* 1995;**108**:1396–404.
- 27 Wakefield AJ, Fox JD, Sawyer AM, *et al.* Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. *J Med Virol* 1992;**38**:183–90.
- 28 Schneider-Schaulies S, ter Meulen V. Molecular aspects of measles virus induced central nervous system diseases. In: Roos RP, ed. *Molecular neurovirology, pathogenesis of viral CNS infections*. Totowa, New Jersey: Humana Press, 1992:419–48.