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Subacute sclerosing panencephalitis: detection of measles virus RNA in appendix lymphoid tissue before clinical signs

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Abstract

An appendix removed 15 days before onset of symptoms of subacute sclerosing panencephalitis was examined retrospectively for measles virus ribonucleic acid (RNA). Tissue sections hybridised in situ to a cloned measles virus probe of deoxyribonucleic acid specific for nucleocapsid protein showed that many cells of the lymphoid tissue contained measles virus RNA. In contrast, only a few infected lymphoid cells were detected in three out of six seropositive controls and none in three seronegative infants.

A widespread chronic viral infection of the immune system, established after measles, may promote or even initiate nerve cell infection in subacute sclerosing panencephalitis.

Introduction

The lymphotrophy of measles virus has recently been described in subacute sclerosing panencephalitis, a delayed neurological disease,

viral ribonucleic acid (RNA) being detected in nerve cells and in both circulating and brain perivascular lymphocytes.¹ We obtained an appendix sample from a patient in whom the first signs of subacute sclerosing panencephalitis appeared after the appendix operation. This afforded an opportunity to examine the interactions between measles virus and lymphoid tissue before the onset of the neurological disease. We report our results using in situ hybridisation and a measles virus specific probe¹ in an attempt to detect viral RNA sequences in the appendix tissue.

Subjects and methods

The patient, a 10 year old girl with a history of measles at the age of 2, underwent appendicectomy for abdominal pain. The appendix was fixed in Bouin's solution and conserved in paraffin. Fifteen days after operation she began to have myoclonic jerks and subacute sclerosing panencephalitis was diagnosed. She died three years after the first manifestation of the disease. Appendix tissue from six subjects seropositive for measles virus and three seronegative newborn infants was used as controls.

Tissue sections (10 µm) were deparaffinised in xylene and dehydrated. After incubation in lithium carbonate they were treated with 0.2M hydrochloric acid and proteinase K² 25 mg/l. The techniques of hybridisation, washings, and autoradiography after six to eight weeks of exposure have been described.¹ The reaction medium contained 0.2 mg probe per l, 200 mg salmon sperm deoxyribonucleic acid per l, and 1 g/l each of CV1 cell RNA, yeast RNA, and *Escherichia coli* RNA.

Results

In tissue taken from the patient before the onset of subacute sclerosing panencephalitis a large number of cells hybridised with the specific viral probe. In lymph follicles (fig (a)) measles virus RNA was found in numerous cells both in the mantle zone and in the germinal centre. Other cells showing hybridisation were present throughout the mucosa, and measles virus RNA was detected in the nuclei of Lieberkühn gland epithelial cells (fig (b)).

Occasional hybridising mononuclear cells were found in blood capillaries where the endothelial cell nuclei also reacted with the probe (fig (c)). Only a

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Sections of appendix tissue from patient with subacute sclerosing panencephalitis (a, b, c) and seropositive control (d). GC=Germinal centre. mz=Mantle zone. Lg=Lieberkühn glands. m=Mucosa. e=Endothelial cells. M=Mononuclear and p=polymorphonuclear cells of capillary. i=Infected cells.

few infected cells were found around Lieberkühn glands in three of the six seropositive controls (fig (d)) and none at all in appendix sections from the three seronegative infants. The specificity of the hybridisation reaction was tested as described.¹

Discussion

These studies show that measles virus RNA may be harboured in appendix lymphoid tissue long after the acute infection both in patients destined to have subacute sclerosing panencephalitis and also, but to a less extent, in normal seropositive subjects.

The large number of hybridising cells present in appendix tissue before the onset of subacute sclerosing panencephalitis correlates with previous observations,^{1,3} and their distribution in the lymph follicles and mucosa suggests that cells of both B and T lymphocyte series are implicated in the infection. Measles virus RNA was also detected in Lieberkühn gland cells and occasionally in capillary endothelial cells, indicating that these cells are sensitive to the virus.⁴ The conservation of viral genetic information found in seropositive normal subjects after measles may be linked to the lifelong immunity present in man.^{1,5}

In subacute sclerosing panencephalitis a widespread infection of the lymphoid system might account for the inability of the host defence mechanism to eradicate measles virus from the brain. Moreover, the system itself would be able to convey the virus into nerve cells by circulating lymphocytes.¹ Thus infection might occur either during acute measles or at any time in the latent phase of subacute sclerosing panencephalitis and possibly just before overt clinical disease develops. Though the pathogenesis of subacute sclerosing panencephalitis remains speculative, the neurotropic feature of measles virus in this disorder appears to be closely linked to its lymphotropic behaviour.

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100 YEARS AGO

A correspondent writes to us:—I should be glad to know whether any steps could be taken by the Board of Health to stop the sale of socks dyed with irritant dyes. I have recently seen several cases in my practice of severe irritation and skin-disease caused by wearing for several days in succession socks—woollen and silk—dyed with bright red and yellow stripes or mixtures, of a colour very attractive to the eye. The eruptions produced have been of a severe character, and, in one case, erysipelatos inflammation. On examining the socks, I found, in two instances, that picric acid was present. It seems to me that steps should be taken to have these "socks of Nessus" examined. Other medical officers of health might, with advantage, look into the matter, and you would render a public service by ventilating the subject. (*British Medical Journal* 1886;ii:729.)