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Infectious Mononucleosis and E.B. Virus Infection

Elizabeth Edmond

Abstract

Infectious mononucleosis has long been an enigma to epidemiologists. The absence of a recognised causal agent or a specific diagnostic test has thrown confusion on such basic issues as the definition of the disease. Until very recently the diagnosis has had to be based on a triad consisting of characteristic signs and symptoms, an absolute increase in atypical mononuclear cells, and a positive heterophile aggultination (Paul Bunnell test) test. Unfortunately each of these criteria is subject to variation in interpretation while the rigid application of the three allows no margin for the diagnosis of subclinical or atypical disease. Within these limits of diagnosis, work on the epidemiology of the disease has produced very few concrete results. While there is no doubt that infectious mononucleosis has a peak incidence in young adults and is relatively uncommon in childhood and older age groups, the evidence concerning infectivity, incubation period and methods of transmission has been circumstantial and often based on a small number of observations. Conclusions drawn from such work suggests that although the disease occasionally develops in contacts it is not highly contagious, and there remains doubt as to whether epidemics of the classical disease have ever occurred. Estimations of the incubation period range between very wide limits, and although there is some evidence that the causal agent is transmitted in saliva (hence the term "kissing disease") the method of natural transmission is still unproven.

Many of these problems of the behaviour of infectious mononucleosis could be solved if a specific causal agent could be recognised and during the last six years the accumulation of evidence implicating the EB virus has caused considerable interest amongst epidemiologists.

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INFECTIOUS MONONUCLEOSIS AND E.B. VIRUS INFECTION

ELIZABETH EDMOND

The Disease

Infectious mononucleosis has long been an enigma to epidemiologists. The absence of a recognised casual agent or a specific diagnostic test has thrown confusion on such basic issues as the definition of the disease. Until very recently the diagnosis has had to be based on a triad consisting of characteristic signs and symptoms, an absolute increase in atypical mononuclear cells, and a positive heterophile aggultination (Paul Bunnell test) test. Unfortunately each of these criteria is subject to variation in interpretation while the rigid application of the three allows no margin for the diagnosis of subclinical or atypical disease. Within these limits of diagnosis, work on the epidemiology of the disease has produced very few concrete results. While there is no doubt that infectious mononucleosis has a peak incidence in young adults and is relatively uncommon in childhood and older age groups, the evidence concerning infectivity, incubation period and methods of transmission has been circumstantial and often based on a small number of observations. Conclusions drawn from such work suggests that although the disease occasionally develops in contacts it is not highly contagious, and there remains doubt as to whether epidemics of the classical disease have ever occurred. Estimations of the incubation period range between very wide limits, and although there is some evidence that the causal agent is transmitted in saliva (hence the term "kissing disease") the method of natural transmission is still unproven.

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The Virus

The Epstein-Barr virus was described in 1964 when it was found to be present in cells cultured from a Burkitt Lymphoma. Its role in the production of the tumour remains an exciting controversial problem which cannot be dealt with here. All attempts to propagate the virus in other types of cell lines have so far been unsuccessful, and only human lymphoid haemopoietic cells will allow the virus to replicate. Antibody to the viral capsid antigen carried in the cells can be detected by an indirect immunofluorescence test described by Henle in 1966. Serological surveys using this technique showed that although antibody to the virus is present in all sera from patients with Burkitt Lymphoma, the antibody is also widely distributed in populations throughout the world regardless of the incidence of the tumour. Thus the incidence of EB viral capsid antibody in some students groups in Edinburgh is shown in Table I.

Table 1 Incidence of EBV antibody in healthy students

Population	Age	Sex	Year sera withdrawn	No. sera tested	% EBV antibody +ve.
1st yr. P.E. College	18	F	1968	55	85
			1969	40	90
			1970	115	85
4th yr. Medical Students	21	M & F	1965	130	71
			1970	122	64
University "Freshers"	18	F	1970	36	72

Table II represents the age incidence of EB virus antibodies in hospital patients in Edinburgh. This is very similar to the age incidence reported from U.S.A., Scandinavia and England, and demonstrates that 32% of children already have antibody by the age of four years.

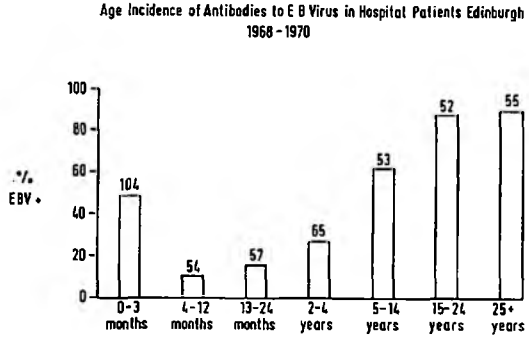

Table II

In order to explain the universal occurrence and common pattern of age incidence of EB virus antibody, attempts were made to link production of this antibody with common infectious diseases. A chance occurrence in the Henle's laboratory in Philadelphia suggested that the antibody might be produced during the course of infectious mononucleosis. In conjunction with workers in Yale who had stored sera from patients with infectious mononucleosis for many years, they were able to demonstrate that sera taken from students before the onset of infectious mononucleosis were devoid of antibody while sera from the same students taken during the acute phase of the disease all had high titres of antibody to the virus. Furthermore, once developed, antibody to the virus persisted for many years, probably for life.

These findings have been confirmed and extended. Recent reports of the finding of macromolecular EBV antibody in the early stages of infectious mononucleosis and one report of the isolation of the virus from the throat of an acute case, make the case against EB virus almost watertight. Despite the doubtful ethics of the problem infectious mononucleosis has been produced on one occasion following injection of virus in a human volunteer.

There remain however many questions to be answered. In particular how is the virus spread?, do healthy carriers exist?, how much, if any, of the heterophile antibody negative disease is caused by EBV?, and what clinical syndromes other than classical infectious mononucleosis can be caused by infection with EBV? The fluorescent antibody test is positive in 80% of normal adults and therefore does not give a specific indication of disease — is the demonstration of EBV IgM antibody helpful in the diagnosis of atypical disease or can other specific tests of current infections be developed?

Edinburgh Student Virus Survey

It was with these unanswered questions in mind that the Edinburgh Student Virus Survey was initiated in October 1971. The survey was brought to the notice of individual students at the time of the matriculation chest x-ray and a sample of venous blood taken from volunteers, who also provided details of previous medical and social history. Sera were tested for antibody to EBV and as a service to female students also to rubella virus. Those students who were without antibody to EBV were requested to attend the Student Health Service again in May, 1972. At the second interview details of any illness occurring in the previous six months were noted and another sample of blood withdrawn for testing. In addition, with the co-operation of the physicians of the Student Health Service serial serum samples have been obtained from students who are unfortunate enough to contract illness which might be infectious mononucleosis.

Female students at Dunfermline College of Physical Education have been taking part in a similar survey started in October, 1970.

Results

Preliminary results of the first year of the survey are shown in Tables III - V.

A total of 613 sera were obtained from university student volunteers and 65% were found to possess antibody to EBV. There appears to be a higher seropositivity rate in the female students.

Table III.

SERA COLLECTED OCTOBER, 1971

	M	F	Total
Nos. of sera screened	322	281	613
No. EBV antibody positive ...	199	200	399
% EBV antibody positive ...	59.9	71.	65.

Table IV.

RESULTS FIRST FOLLOW UP (May 1972)

No. of 2nd sera available	164
No. EBV antibody positive	18
% Conversions	11

Table V Incidence of Illness in Initial Seronegative Group

Group	Total No.	Proven or suspected I.M.	Other symptoms	No symptoms
Sero-conversions	18	5	6	7
Persistent seronegatives	146	0	54	92

After approximate seven months of academic life 18 of those students initially seronegative were found to have produced EBV antibody, giving a conversion rate of 11%.

Table V shows that of the 18 students known to have acquired EBV antibody in the seven months following their entry to university, 5 (28%) had been investigated as possible cases of infectious mononucleosis, while 7 (39%) had no symptoms of any kind. Other symptoms, mainly sore throats, were reported by 6. In contrast none of the 144 volunteers who remained seronegative were suspected of having infectious mononucleosis.

A small number of sera from patients in the acute phase of infectious mononucleosis have been investigated in this first year. It has been found that by the time the patient presents with symptoms, antibody to EBV measured by the fluorescence method is already present at high titre, and little change can be detected during the course of the illness. Antibody measured by the complement fixation reaction however appears to rise much more slowly and may not become positive until several months after the illness. If this is true then a combination of fluorescence antibody and complement fixing antibody may give a valuable indication of the timing of infection.

It is hoped that this, and many other aspects of the disease will be clarified in the next two years of the survey. The numbers involved at this stage are still small but in October 1972 a further 1,000 students have volunteered to take part. We would like to take this opportunity of thanking all our student volunteers and look forward to providing more details of the results at some future date.