Seroepidemiological Study of Infectious Mononucleosis in Older Patients

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In southern Tasmania, Australia, primary Epstein-Barr virus infection occurs in adults >30 years of age at a higher frequency (~13% of all cases) than is generally reported for other parts of the world, and ~7% of the general population of the region have no antibodies to the virus. Epstein-Barr virus should not be overlooked as a possible cause of disease in older patients in similar populations elsewhere.

Epstein-Barr Virus (EBV) is the cause of heterophile antibody-positive infectious mononucleosis (HA+ IM). This is predominantly a disease of adolescents and young adults. Cases in patients >30 years old have been reported to occur at a frequency of 3% or less (4, 7, 8).

The diagnosis of IM in its classic form is based on clinical, hematologic, and serologic (presence of HA of the Paul Bünnell type) criteria (3). For atypical cases and for epidemiological studies, EBV-specific serodiagnostic tests are of value. Four antigens are currently of importance: the viral capsid antigen (VCA), virus-induced early antigens subdivided into the diffuse and restricted components, and the EBV-associated nuclear antigen (EBNA) (6).

In 1986 and 1987, we reviewed the incidence of HA+ IM in southern Tasmania and found an unexpectedly high proportion of apparent HA+ IM in patients over 30 years of age. EBV-specific serologic investigations of the general population and IM patients were consequently performed in an effort to evaluate the significance of this finding and the value of the HA test in the diagnosis of primary IM in older patients.

The southern region of Tasmania, the island state of Australia, has a population of approximately 205,740, (102,147 >30 years of age) and is serviced by three pathology laboratories from which data on all patients presenting for the first time with strongly positive HA tests (Monospot; Ortho Diagnostics, Inc., Raritan, N.J.) were collected.

There were 375 patients in 1986 and 422 patients in 1987. Details of age and sex could not be obtained for 20 and 39 of these patients, respectively, and these were excluded from the survey. All patients had symptoms and/or a blood count suggestive of IM, which prompted the initial HA testing. Monospot tests and blood counts were examined by one of a small number of medical scientists or pathologists.

The majority (88% [265 of 300] in 1986 and 83% [274 of 330] in 1987) of patients <30 years of age had blood counts typical (>50% lymphocytes, >10% atypical) of or consistent (<50% lymphocytes, >10% atypical) with the diagnosis of IM at presentation. However, the corresponding figures for the patients >30 years old were 62% (34 of 55) and 64% (25 of 39). Liver and blood complications at the time of initial HA testing showed no correlation in either year with the age and sex of the patients, being spread evenly over all groups. None of the patients had received a blood transfusion in the past year.

A peak incidence in the adolescent age group was found in both years, as expected. However, a significant "tail" of HA+ sera was observed in the >30-year-age groups (55 of 355 [15%] in 1986; 43 of 383 [11%] in 1987) (Fig. 1). There was no seasonal variation in incidence, and the distributions were similar for both sexes.

It is unlikely that cases in the older age groups were the result of false-positive Monospot tests. Although false-positive results are encountered occasionally in patients with underlying disease (leukemia, lymphoma, rheumatoid arthritis, hepatitis), they occur at a low rate (<1%) (3). To our knowledge, the vast majority of older patients in this study were free of these conditions. Two patients only (in 1986) with severe symptoms of viral hepatitis and for whom tests by the laboratories for EBV-specific immunoglobulin M (IgM) at the time of HA testing were negative were considered to be false-positive. The true incidence of symptomatic infection caused by EBV in older patients may well be even higher than estimated above. With a low index of suspicion, HA testing may not have been performed on some symptomatic older patients. Also, patients with atypical symptoms or initially normal blood counts or patients in whom HA is absent or slow to develop would have been missed. These properties may be more common in older patients (2, 7, 10, 13).

Since the epidemiological survey was largely a retrospective one, sera from most patients were not available for specific EBV antibody testing. Sera were, however, collected from HA+ IM patients towards the end of 1987 and in early 1988 from both adolescent (n = 23) and older (n = 14) groups. Although only 62% (23 of 37) had blood counts typical of or consistent with IM, all had high VCA IgM titers (majority, ≥320) (Gull Laboratories, Salt Lake City, Utah). VCA IgG was also detected (the vast majority had titers of ≥40) (Electro-Nucleonics Inc., Bethesda, Md.). Sera were all negative for rheumatoid factor (Rheumatin; Carter-Wallace, Frenchs Forest, New South Wales, Australia) and cytomegalovirus IgM (Gull). Only one patient (aged 34 years), who was subsequently diagnosed with acute myeloid leukemia, had detectable levels of anti-EBNA antibodies (Gull).

Thus, virus-specific serology strongly suggests that the vast majority of patients, young and old, experienced a primary infection. Symptomatic disease caused by chronic or reactivated EBV infection is still a controversial issue (1, 9, 15), but it is unlikely that the majority of patients in our study would fall into these categories. IgM to VCA is not usually found as a feature of chronic illness, and since our patients presented with HA antibodies for the first time, it is...
likely that symptoms were only recently acquired. In reactivation of latent virus, VCA IgM may be present. Specific IgM responses in reinfection with rubella virus, herpes simplex virus, and varicella-zoster virus have been reported (11, 12, 16), and Sumaya has reported similar findings with EBV (17). EBNA antibodies would usually be detectable in such cases. The patient with acute myeloid leukemia was the only patient with evidence suggestive of past exposure to EBV.

The results of a serologic survey to determine the level of exposure to EBV in the general community of southern Tasmania are shown in Fig. 2 and 3. A total of 246 serum specimens were obtained (from 134 control patients presenting for blood tests unrelated to infection and 112 volunteer blood donors, Red Cross Transfusion Service, Tasmania). The incidence of VCA IgG was approximately 93% overall, only slightly lower than that reported in the majority of other centers (3, 4, 14). Antibody titers tended to be high (~75% of serum specimens, ≥320) (Fig. 2 and 3), with similar distributions in males and females. Nevertheless, approximately 14,402 individuals in the region are at risk of primary infection, and half of these are over 30 years of age.

No difference was observed in the antibody prevalence rates for the two groups tested, the first representing a broad cross section of society drawn from the same population group as the HA+ patients and the second representing a group which might be expected to represent a greater proportion of individuals from upper and middle socioeconomic classes.

A sample (n = 56) of these sera was subsequently tested for EBV VCA IgM. Four of 56 serum specimens were positive, and these were all from pathology laboratory patients with high titers of IgG to EBV VCA (≥640). All four IgM-positive specimens were negative in tests for HA, EBNA (1:10), rheumatoid factor, and cytomegalovirus IgM. One specimen was positive for EBNA at a 1:5 dilution. On review, two of these patients had reported fatigue, fever, and mild pharyngitis at the time the serum was obtained and were probably experiencing a mild EBV infection. The majority (57% [25 of 44]) of the IgM-negative samples with high IgG titers showed strong fluorescence in the anti-EBNA test at the screening dilution (1:10). Samples (n = 22) with low IgG titers (<40) were all EBNA negative.

Evans et al. (5) have estimated that only ~1.3% of the general population is positive for VCA IgM. Our results support this. However, since VCA IgM may be present in asymptomatic or mild HA+ cases, in reactivation of latent virus, and sometimes in chronic disease, there is a limit to its usefulness as a single diagnostic test. The HA test is more useful as a screen, with the IgM test used to confirm the role of EBV in patients whose blood counts may not initially show features diagnostic of IM. The HA test appears to be a reliable guide to EBV infection on the basis of the specific antibody tests done with the patients in this study.

Tasmania provides an ideal situation for epidemiological studies, since patient records and laboratory results for a well-defined population area can be accurately collected. Our results show that IM caused by primary EBV infection may be more common than is generally thought in older patients in areas such as southern Tasmania, where a large proportion of the population reaches adulthood without having been exposed to the virus. It is also interesting to speculate whether there is a relationship between delayed exposure to EBV and diseases, such as multiple sclerosis, lymphomas, and autoimmune disorders, which also have a
high prevalence in Tasmania and in which elevated levels of EBV-specific antibodies are seen (18, 19).

LITERATURE CITED