

Fatal mononucleosis? Don't rule it out

A low index of suspicion on the part of clinicians and pathologists may be a factor in some cases of fatal infectious mononucleosis.

Though not common, mortality from this disease is not unheard of (*JAMA* 236:1493-1494, 1976). In fact, David T. Purtilo, MD, professor of pathology and pediatrics at the University of Massachusetts Medical Center, Worcester, believes that there are no fewer than 30 to 35 such cases in the United States each year, a figure that exceeds the combined number of cases of poliomyelitis, fatal rabies, and several other diseases considered more dangerous than infectious mononucleosis.

Until 1970 only 20 fatalities in which there was clinical, hematological, and serological evidence of infectious mononucleosis had been reported. But during the ten-year period ending in 1976, said Purtilo, 195 cases were recorded by the Center for Disease Control, Atlanta, notwithstanding the fact that infectious mononucleosis is not a reportable disease.

The problem, Purtilo said at the recent meeting of the International Academy of Pathology in New Orleans, is misdiagnosis and lack of understanding of the potential seriousness of the disease. Even when specimens of hematopoietic tissue from patients with lingering signs and symptoms are sent to the laboratory, pathologists may not recognize the characteristic immunoblastic proliferation with mononuclear cell differentiation to plasma cells and reactive macrophages.

Infectious mononucleosis is actually a common illness. Upwards of 2% to 3% of the population will have recognizable infections during their lifetimes. A much higher percentage—up to 90% of children—will have silent infections.

Mismanagement may come about when the physician does not attend sufficiently well to continuing illness. "In fact," Purtilo told *JAMA MEDICAL NEWS*, "I've been consulted on litigation. There have been three or four lawsuits alleging negligence because of fatal mononucleosis, in which the doctor said, 'The child's going to get well.' These doctors weren't told that Epstein-Barr virus [EBV] infection can prove fatal."

Purtilo described seven representative cases from major medical centers in which there were fatal complications. In addition to the more familiar splenic rupture with exsanguination (*JAMA* 240:1752, 1978), the complications included pulmonary embolism and infection, massive hepatic necrosis with hemorrhage, renal failure from lymphoid infiltration, and conversion to malignant lymphoma.

Which Patients are Susceptible?

But his presentation at the meeting engendered some skepticism. John Newby, MD, head of clinical pathology at the US Naval Hospital in Portsmouth, Va, noted that his hospital clinics see "a lot of young men and women with clinical mononucleosis. They're

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basically healthy, and we haven't seen any fatal or even near-fatal cases. Could it be," he asked, "that the entity of fatal mononucleosis is *always* one reflecting an underlying immunodeficiency or genetic deficiency?"

Purtilo concedes he doesn't yet know the whole answer. Along with coresearchers John L. Sullivan, MD, and Louise A. Paquin, PhD, he is beginning to delve into the family histories of more than 60 such persons who have died. He has also established a registry at the University of Massachusetts Medical Center of fatal infectious mononucleosis and other EBV infections (see LETTERS TO THE EDITOR, page 1806, this issue).

But it does seem that lethal complications of mononucleosis are more frequent in patients who are immunologically incapable of containing the infection or have other immunological deficiencies. Specifically, predisposition to complications has been found in persons with a rare disorder, the X-linked lymphoproliferative syndrome (*JAMA* 241:998, 1979). In addition, maternally related males of several of the patients Purtilo described seem to have a high incidence of malignant lymphoma.

Moreover, a number of the lethal complications of infectious mononucleosis may be explained on an apparent autoimmune basis. "Heuristically," notes Purtilo, "infectious mononucleosis mimics graft-vs-host disease." Skin rash, hepatitis, and hypergammaglobulinemia—some of the features that are seen with graft-vs-host disease in humans and experimental animals—also occur in many patients with infectious mononucleosis.

"This virus is very strange," remarked co-researcher Sullivan. "It is the only virus that has such a selective cellular tropism. That is to say, it damages only the B lymphocytes—not macrophages, T lymphocytes, or polys."

Sullivan cites 14 instances in which adolescent boys who survived an initial insult with EBV were shown to have subsequent immunological deficiencies compatible with loss of the B cell population. It is possible that a self-destructive process begins when EBV alters membrane antigens on the B lymphocytes, a process that in some way results in the formation of autoantibodies.

But Sullivan is quick to point out that even in the face of good host immunity—a negative history of abnormal reactions to immunizations, of repeated infections, or of gross immunodeficiency—EBV can have an invasive course. He cites the case of a previously healthy boy in whom bone marrow suppression and encephalitis developed during an EBV infection. He was treated with large doses of steroids and subsequently died of staphylococcal septicemia.

What is the origin of the term "infectious mononucleosis"? John L. Sullivan, MD, believes the name was coined by Thomas P. Sprunt and Frank A. Evans in a 1920 article (*Johns Hopkins Hospital Bull* 31:410-417). The report was entitled "Mononuclear Leukocytosis in Reaction to Acute Infection ('Infectious Mononucleosis')," and the "infectious" label indicated that the illness was associated with an acute infection, not that it was necessarily contagious.

"I don't think there's any question," said Sullivan, "that EBV is capable of producing a whole variety of clinical syndromes, from Guillain-Barré syndrome and Bell's palsy to thrombocytopenia. Like other viruses, it can produce severe hepatitis and acute yellow atrophy with liver failure that results in death."

Confirming the Diagnosis

Accordingly, he believes the clinician should maintain a higher index of suspicion for EBV infections, especially among persons in the second and third decades with recurrent infections and lingering symptoms and signs of infectious mononucleosis. The slide test for infectious mononucleosis heterophile antibodies (Monospot) is a good screening test, he believes, but if negative, it should be repeated the following week if certain signs and symptoms continue. If it yields positive results, the physician should inquire of the laboratory whether the differential absorption test indicates that the heterophile antibody is specific for infectious mononucleosis (the point being that noninfectious heterophile antibody can occur in other diseases, such as serum sickness and lymphoma).

A heterophile antibody screen can be ordered next, but for confirmation (in chronic or otherwise complicated cases) specific serological tests for EBV are required. Such a test can be performed either by the laboratory of Drs Gertrude and Werner Henle at Children's Hospital, Philadelphia, or by Purtilo and Sullivan's laboratory at Worcester. Pathologists may also look to these laboratories for the most refined corroborating tests—demonstration of the actual presence of the virus by EBV nuclear antigen immunofluorescence or EBV-DNA hybridization. However, to perform these tests frozen tissue is required. "Once you throw it in formalin," says Purtilo, "the ball game's over."

Above all, a good family history for evidence of immunodeficiency conditions is warranted.

—by ALAN BLUM, MD, Morris Fishbein Fellow