Out of Africa: Retrovirus Linked to Autoimmunity

BY NANCY WALSH
New York Bureau

BIRMINGHAM, ENGLAND — A newly identified human endogenous retrovirus that is much more prevalent in Africa than in other parts of the world may place its carriers at risk for certain autoimmune diseases, David Moyes, Ph.D., said at the joint meeting of the British Society for Rheumatology and the German Society for Rheumatology.

Patients with autoimmune diseases often have elevated antibody levels to certain structural proteins of human endogenous retroviruses (HERVs), suggesting a possible role for these viruses in autoimmune disease, Dr. Moyes said.

Until recently it was thought that HERVs were ubiquitous and fixed in the population, having been incorporated into the genome before the initial wave of human migration out of Africa some 200,000 years ago. But two of these viruses, HERV-K113 and HERV-K115 are now known to vary widely in prevalence across different populations. "This means that both viruses are likely to have been incorporated into the genome during more recent human evolution and that both could potentially induce an autoimmune response," he said.

In 96 patients with Sjögren's syndrome, the prevalence of the K113 allele was significantly increased, at 16%, compared with 4% among 96 controls.

The mean prevalence of HERV-K113 identified by polymerase chain reaction testing in a sample of 174 subjects from Kenya, Malawi, and Côte d'Ivoire was 22%, compared with 4% in a sample of 96 subjects from the United Kingdom, said Dr. Moyes of the Kennedy Institute of Rheumatology, Imperial College, London.

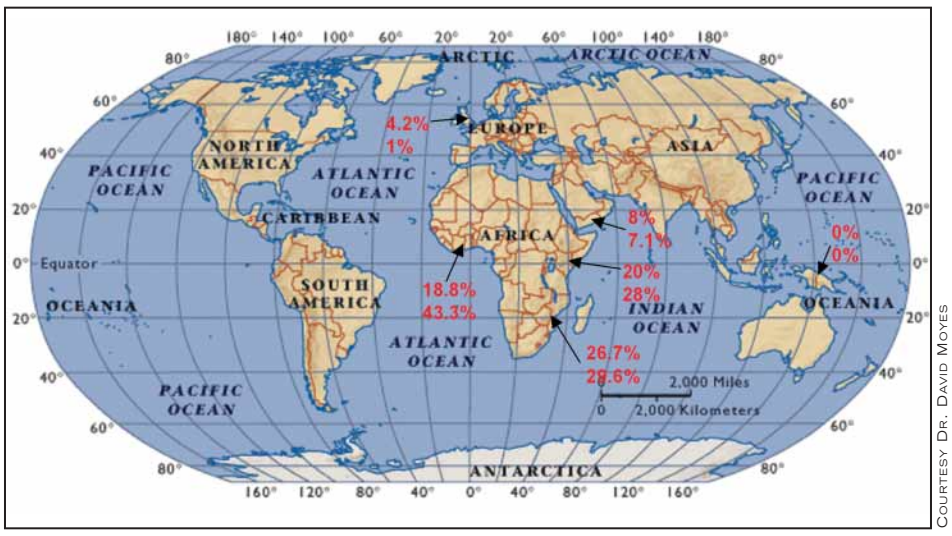
Similarly, HERV-K115 was present in 34% of subjects from Africa and in only 1% of those in the United Kingdom.

"When you move off the African continent to the Arabian peninsula the prevalence drops off markedly. Neither virus was detected in any of 54 samples from Papua New Guinea," he said.

"Because of the possibility that one or both of these retroviruses could be involved in autoimmune disease, we went on to analyze their prevalence in two U.K. disease cohorts," he said. Among 96 patients with Sjögren's syndrome, the prevalence of the K113 allele was significantly increased, at 16%, compared with 4% among 96 normal controls. The allele also was more prevalent among 100 patients with multiple sclerosis, at 12%, he said.

Increases in these diseases were not associated with K115, however, which is a defective virus. "Both are full length proviruses, but HERV-K113 is a complete virus that has open reading frames and can fully express all its genes. HERV-K115 has a single deletion that prevents the expression of the *Pro/Pol* genes," he said.

An audience member asked if there was any evidence that these viruses were pathogenic, and whether there was an association with the autoantibodies Ro and La that are present in many autoimmune diseases. Dr. Moyes replied that there does not appear to be an association with Ro and La specifically, but that there is an increase in many other autoantibodies seen in patients with scleroderma, rheumatoid arthritis, and Sjögren's syndrome. "The exact relevance of those increases is open to question, but there is also a degree of evidence suggesting that proteins from these viruses can induce inflammation," he said. ■



Courtesy Dr. David Moyes

The upper number is the prevalence of human endogenous retrovirus (HERV)-K113 in each country. The lower number is the prevalence of HERV-K115.

Study Links Lupus to a Range of Pulmonary Complications

BY NANCY WALSH
New York Bureau

LONDON — Long-term follow-up of the 1,500-patient Johns Hopkins lupus cohort is providing some much needed data about the profile and natural history of pulmonary disease in patients with systemic lupus erythematosus, according to Michelle Petri, M.D.

Pleurisy is the most common pulmonary manifestation of lupus, with a prevalence of approximately 40%-60%. The majority of patients who ever experience pleurisy have their first episode within a year of their lupus diagnosis, Dr. Petri said at the Sixth European Lupus Meeting.

The condition, which can be unilateral or bilateral, is more common among African Americans and is often accompanied by fever and lymphadenopathy. Patients also typically have other manifestations of lupus such as Raynaud's phenomenon, arthritis, and cardiac murmurs, said Dr. Petri, professor in the division of rheumatology, Johns Hopkins University, Baltimore.

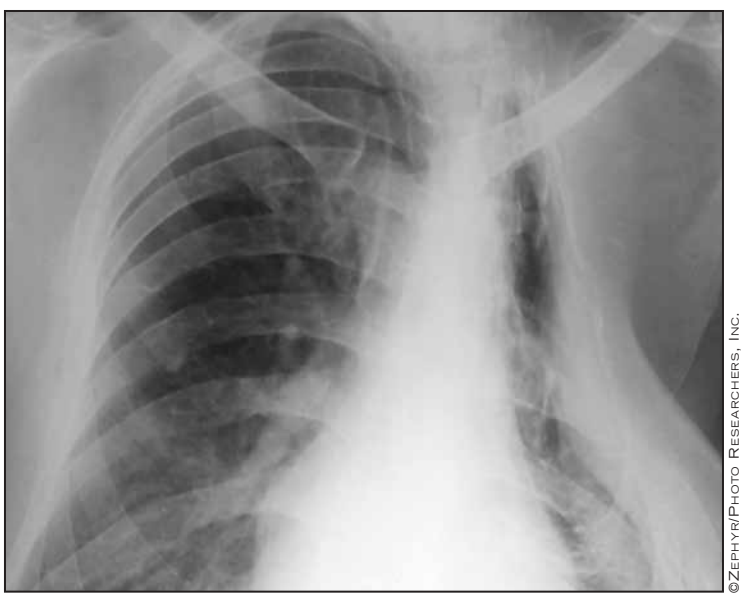
"Once patients develop pleurisy, our cohort database suggests they are going to have other pulmonary problems, including pneumonitis, pulmonary hypertension, and pneumonia," she said.

With acute lupus pneumonitis—a rare but dangerous complication—patients present with fever, dyspnea, tachypnea, and hemoptysis. "Your job in the first 24 hours is to treat and rule out infection at the same time," Dr. Petris said at the meeting, which was sponsored by the British Society for Rheumatology.

Lung biopsy is often required, and findings include a diffuse lymphocytic infiltrate, lymphoid nodules, and bronchiolitis. "There also is deposition of both immunoglobulin and complement, which proves this is an immune-complex–mediated condition," she said.

In one early series, 50% of patients with lupus pneumonitis died (Medicine [Baltimore] 1975;54:397-409). "That has not been my experience. My patients have done well when treated aggressively with intravenous pulsed methylprednisolone therapy," she said. If the patient does not stabilize within the first 48 hours and infection has been ruled out, usually with a bronchoscopy, intravenous cyclophosphamide is begun.

Another rare and equally dangerous manifestation is pulmonary hemorrhage, where patients present with fever, dyspnea, cough, and blood-tinged sputum. This condition is usually rapidly progressive, with a dramatic drop in hematocrit and bilateral pulmonary infiltrates. Diagnosis may require bronchoscopy, MRI, or CT, she said.



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Chest x-ray shows a large area of pleurisy, the most common pulmonary manifestation of lupus, obstructing the lung at right.

Treatment is similar to that for acute lupus pneumonitis, but with the addition of plasmapheresis in patients who do not stabilize. Prognosis is not good, with reported survival rates ranging from 50% to 75%.

"Pulmonary embolism is something we all have seen." In addition to their tendency to develop nephrotic syndrome, their antiphospholipid antibody and homocysteine levels may also contribute to making them hypercoagulable.

"In our cohort data we found that, if lupus anticoagulant was present at the time of diagnosis, the patient had about a 50% chance of having a venous thromboembolism within the next 20 years," she said.

Prevention is key in these patients, and includes some simple measures like avoiding oral contraceptives in patients with lupus anticoagulant at the time of diagnosis. "But prospective data from our cohort show that patients who are on hydroxychloroquine at more than 50% of their clinic visits had a remarkable reduction in venous thrombosis, with an odds ratio of 0.36," she said.

Hydroxychloroquine may have a beneficial effect by lowering titers of antiphospholipid antibodies, and/or by reducing thrombus size.

Pulmonary hypertension is increasingly recognized as a complication of lupus. The condition usually is mild and most commonly seen in patients who also have Raynaud's phenomenon. In one series, mild pulmonary hypertension was detected in 14% of patients, but 5 years later that number had increased to 43%. "There's a lot of mild pulmonary hypertension out there, and with greater survival among lupus patients this is going to become more of a clinical issue that we will have to address," she said.

Most of these severe pulmonary complications of lupus fortunately are rare, but the rarity itself presents challenges. "The only way we are going to make progress with these rare manifestations is through collaboration between all the lupus cohorts worldwide," she said. "We need that, and we needed it yesterday." ■