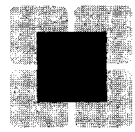

WILLIAM S. WILKE, MD, EDITOR

EOSINOPHILIA-MYALGIA SYNDROME: UNRESOLVED QUESTIONS

L-tryptophan, widely accepted for years as an over-the-counter remedy for insomnia, made headlines recently when it was linked to a syndrome characterized by eosinophilia, myalgia, and a wide variety of other symptoms and laboratory signs. As of February of this year, 1,300 cases had been reported in the United States, three of them fatal.

L-tryptophan has since been removed from the US market and we can expect that the prevalence of eosinophilia-myalgia syndrome related to the drug will decrease. Nevertheless, our understanding of the mechanisms and pathogenesis of the disease will continue to evolve for months to come as we evaluate the resulting literature and epidemiologic data.

DIAGNOSTIC CRITERIA

The Centers for Disease Control has defined these surveillance criteria for the diagnosis of eosinophilia-myalgia syndrome: eosinophil count equal to or greater than 1,000 cells/mm^3, myalgia severe enough to limit normal activity, and exclusion of other infectious or neoplastic illnesses that could account for the eosinophilia or myalgia.

The syndrome has a broad spectrum of other manifestations, including arthralgia, dyspnea, cough, pulmonary infiltrates, vasculitis, and a variety of skin rashes that usually involve the extremities. Edema may be seen and some patients may have a fever up to 40°C.

Most patients have a high white blood cell count and elevated aldolase, but few have elevated levels of creatine phosphokinase. Elevated liver function tests, pleural effusions, and elevated immunoglobulin E levels are common.

To obtain an accurate eosinophil count, it is necessary to do a differential and multiply the proportion of eosinophils by the total count; in addition, one should use a specific stain, such as Discombe's solution. The upper limit of normal in an adult is 125 to 250 cells/mm^3. A level greater than 500 cells/mm^3 is considered to be eosinophilia.

The eosinophil level in the peripheral circulation is only a fraction of the level in tissue and other body sites. The number of eosinophils in tissues may be three to five times greater than the level in the peripheral blood. This characteristic distinguishes eosinophils from neutrophils, which normally do not infiltrate healthy tissues. Therefore, even if the peripheral eosinophil count is normal, there may increased counts in the lung or skin tissue, which can be revealed on biopsy.

DIFFERENTIAL DIAGNOSES

The patient who presents with eosinophilia and myalgia should not be assumed to have the L-tryptophan-related syndrome until other likely diagnoses have been ruled out. For example, a travel history will help to exclude the presence of helminthic infections. Eosinophilia tends to develop primarily in the tissue-invasive phases of helminthic infections; those that involve the gastrointestinal tract only are not usually associated with a high degree of persistent eosinophilia. Visceral larval migrans, which is caused by hookworms of dogs and cats, should be considered in children.

Immunologic causes include allergy, hypersensitivity vasculitis, and pulmonary infiltrates with eosinophilia. Idiopathic hypereosinophilic syndrome is a major diagnosis to be excluded. Although these patients tend to have more significant thromboembolic and neurologic manifestations, it may not be possible to rule it out completely.

Neoplastic disease can cause eosinophilia and myalgia, but these disorders usually have clearcut features that distinguish them from other diagnoses.

PATHOGENESIS

Eosinophilia-myalgia syndrome is linked unquestionably to the ingestion of L-tryptophan, but some affected patients had used the pills for 2 weeks or less, while others had been taking them for more than 15 years before the syndrome developed.

No toxic metabolite has been isolated. Case-control studies have linked several different lots from the same Japanese manufacturer to patients with the syndrome. It may develop that a toxic product is involved that is completely unrelated to L-tryptophan or its metabolites. Alternatively, there may have been a contaminant that

by itself was not toxic, but that may have inhibited or altered these patients' ability to metabolize the large amount of ingested L-tryptophan.

L-tryptophan is metabolized via either the 5-hydroxytryptamine or the kynurenine pathway; both depend on vitamin B6, or pyridoxal phosphate, as a cofactor. It has been theorized that an abnormality in the kynurenine pathway may be responsible for the syndrome, but the specific abnormality has not yet been identified.

Investigations have also raised questions about whether the syndrome has an immunologic pathogenesis. For example, in humans, IgE production and eosinophilia are controlled by two predominant cytokines, interleukin-4 (IL-4) and interleukin-5 (IL-5), respectively. T helper cells that have been triggered by various antigens may produce two cytokines. IL-5 activity in particular leads to eosinophil differentiation and proliferation in the bone marrow and to eosinophilia. Since individuals with idiopathic hypereosinophilic syndrome have lower than expected levels of IL-5 produced by their T cells, it appears that additional non–IL-5 dependent mechanisms may account for eosinophilia in some situations. We do not know yet how eosinophila is regulated in the eosinophilia-myalgia syndrome.

MANAGEMENT

The primary treatment is to make certain the patient stops ingesting L-tryptophan and, in cases of mild illness, to follow the patient closely. In severe, aggressive disease, high-dose (60 mg/d) prednisone therapy is recommended for several weeks. Cytotoxic drugs such as hydroxyurea and cyclophosphamide may have a role in the treatment of patients who have progressive neurologic manifestations.

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SMOKING CESSATION: STRATEGIES THAT WORK

Physicians tend to perceive smoking cessation as an unreachable target; yet, most patients who smoke will eventually quit in response to repeated, persistent support and encouragement from a physician.

When patients visit physicians, they are concerned about their health, and therefore receptive to suggestions that will improve or maintain it. A group of Minnesota physicians (Doctors Helping Smokers) has acted on this phenomenon and had remarkable success. Furthermore, they have been able to translate their smoking cessation success rate into decreased use of health care services and lower health care costs.

The Doctors Helping Smokers program is distinguished by persistence. Many clinicians, unconvinced of their influence on patients who smoke, neglect to follow through after telling patients that smoking is dangerous and they should quit. Yet, simple, brief, one-time physician's advice to quit smoking produces long-term (1 year or more) quit rates of 3% to 9%. Adding specificity to the message and providing follow-up can result in quit rates of 10% to 27%. The Minnesota program recognizes the need for this continued support and encouragement, but also appreciates the time limitations of day-to-day practice.

The program works as follows: All patients are screened for smoking status. At every encounter with a smoking patient, after addressing the primary problem, the doctor says, "I want you to stop smoking," and follows that with "Are you ready to stop now?" and "When will you be ready to stop? On what day?"

Patients are urged to name a stop date, and the physician then asks if they would like help to stop smoking. Patients who say yes are referred to smoking cessation programs. With or without a referral, patients are told that a nurse will call 3 to 7 days after the stop date to check on their progress and find out whether they need help. Careful records are kept of the patients' responses, and follow-up continues at least every 3 months.

PHYSICIANS HAVE MORE INFLUENCE

The Minnesota program has shown that a physician's recommendation to quit has an impact on the patient, particularly when it is repeated on several occasions, and when information about health dangers is related directly to the patient from the physician.

Most patients who smoke know about the associated dangers; but the effect of hearing about them from children, spouses, friends, and the media pales in comparison