Chronic Beryllium Disease: Uncommon Disease, Less Common Diagnosis

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Chronic beryllium disease (CBD) is typically considered only when occupational exposure to beryllium is a certainty; however, CBD has also occurred in occupational and environmental settings where exposure was unexpected. When the etiology of a case of granulomatous pulmonary disease is not determined, sarcoidosis is the "diagnosis of exclusion." This diagnosis does not communicate much information about the patient's prognosis, the disease's etiology, or even what disease etiologies were specifically excluded. Some cases of CBD have been called sarcoidosis, allowing exposure to continue for the patient and (at times) other individuals. The granulomatous changes of sarcoidosis are thought to result from an abnormal immune response. While the etiologic agents that can initiate this response are largely unknown, the immunopathogenesis of CBD has been well described, and laboratory methods are available in a few centers that can (if used) identify beryllium hypersensitivity. The potential for exposure and disease to be widely separated in time and location makes it important for health-care and environmental health professionals to be aware of these new diagnostic methods. *Key words*: berylliosis, beryllium, granulomatous, hypersensitive, lymphocyte, pulmonary, sarcoidosis. *Environ Health Perspect* 106:765–767 (1998). [Online 2 November 1998]
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Beryllium-induced lung diseases can usually be categorized as either an acute or a chronic disease process. After briefly reviewing acute beryllium disease (ABD), this paper reviews chronic beryllium disease (CBD) and explores state-of-the-art diagnostic advances.

Acute Beryllium Disease

Inhaling high concentrations of beryllium can lead to acute chemical pneumonitis with dyspnea, cough, and chest pain. Physical examination of these patients reveals tachypnea with inspiratory rales and tachycardia. Pulmonary infiltrates are usually seen on the chest X ray, and arterial blood gases typically reveal hypoxemia (*1*). This acute process has occasionally resulted in death; if the patient survives the acute illness, recovery is typically complete.

The first cases of ABD in the United States were reported in 1943; the exposures occurred while workers were extracting beryllium oxide from beryllium ore. The physicians reporting these cases were initially unsure about the role of beryllium, concluding that the chemical pneumonia in three workers was due to "chemical compounds formed outside or inside the respiratory tract during the processing of the ore" (*2*).

By the time of a follow-up report in 1945 (*3*), this group of researchers had seen 170 cases of acute beryllium poisoning. In these cases, the symptom complexes included dermatitis, chronic skin ulcers, and pneumonitis; five of these workers had died. With advances in industrial hygiene, ABD has been virtually eliminated in the United States: there were 53 acute cases reported in 1947, 28 in 1948, and 1 in 1949 (*4*).

A committee of experts was assembled in 1950 by the Atomic Energy Commission to recommend safe levels of beryllium in air (*4*). Other than rare cases resulting from accidental exposures, ABD is no longer a problem in the United States.

Chronic Beryllium Disease

While ABD is mostly of historical significance in this country (*5*), cases of CBD continue to occur. The inflammatory process of CBD is characterized by the formation of noncaseating granulomas that contain predominantly epithelioid cells and lymphocytes. While case reports have included other organ systems, the lungs are the primary site of involvement. An unknown number of CBD cases are not properly diagnosed (*6*).

Most cases of CBD result from prolonged or multiple ambient exposures to beryllium. When exposure is uncertain, it is sometimes possible to demonstrate excess beryllium in biopsy specimens from the lung using laser microprobe mass spectrographic analysis.

The symptoms that cause the patient to seek medical evaluation can include arthralgias, chest pain, cough, or (most commonly) dyspnea with relatively mild exertion. Physical examination may reveal hepatosplenomegaly, inspiratory rales, and lymphadenopathy. The chest X ray typically reveals diffuse infiltrates and frequently reveals hilar lymphadenopathy. Computed tomography can accurately characterize the extent of disease, but cannot reliably differentiate between CBD and sarcoidosis (*7*). Pulmonary functioning (especially exercise tolerance) eventually becomes abnormal, although air flow patterns can be restrictive, obstructive, or even normal with a reduced diffusing capacity (*8*).

CBD is a progressive disease that often requires treatment with corticosteroids for life. Preventing additional exposure is an important aspect of therapy, but does not arrest the disease process in most patients. In one sense, exposure continues: beryllium deposited in the patient's lungs provides persistent antigenic stimulation over time (*9*).

Epidemiology of CBD. The first cases of CBD in the United States were reported in 1946; these exposures occurred while workers were manufacturing fluorescent lamps. The U.S. Beryllium Case Registry (currently inactive) was established in 1952 at the Massachusetts Institute of Technology and maintained after 1978 by the National Institute for Occupational Safety and Health (NIOSH). This registry contains approximately 900 cases of CBD; entering a case into the registry required documentation of beryllium exposure, either by history or by demonstration of excess beryllium in biologic specimens, plus any three of the clinicopathologic criteria summarized below (*10*):

1. Clinical symptoms of a lower respiratory tract disorder
2. Reticulonodular infiltrates on chest radiography
3. Restrictive or obstructive impairment of pulmonary function or a depressed diffusing capacity for carbon monoxide
4. Histologic demonstration of noncaseating granulomas and/or mononuclear cell interstitial infiltrates on lung biopsy specimens.

The number of CBD cases that could meet the definition, but were not identified and added to the registry is unknown. There is evidence that sarcoidosis is diagnosed without adequately excluding CBD (*6*). Also, researchers using modern laboratory methods have shown that some patients who do not meet the registry criteria do have CBD (*11*). After taking a thorough exposure history, the clinical diagnosis

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of CBD can be adequately supported by demonstrating both pulmonary granulomas and immune responsiveness to beryllium.

Besides occupational cases of beryllium, the registry also contains 65 nonoccupational (environmental) cases reported before 1960: 23 cases resulted from exposure to dust brought home on work clothes and 42 cases resulted from off-site air pollution. With improvements in industrial hygiene, environmental cases of CBD were thought to have disappeared. However, Newman and Kreiss (*12*) recently reported a case that resulted from what appeared to be a brief, low-level exposure; this report suggested that although environmental cases are rarely diagnosed, they do occur.

Immunology of CBD. The early health studies of beryllium were difficult to interpret because the dose that produced disease appeared to vary considerably, disease severity did not correlate with tissue levels, and the latency period was often long (*13,14*). These characteristics lead (as early as 1951) to the postulation of an immune mechanism (*15*); however, because beryllium has a very low molecular weight, this ability to induce an immune response was unexpected. Much of the research on CBD has focused on understanding this immune response and developing a reliable test for beryllium hypersensitivity (*16*).

In 1951, cutaneous hypersensitivity to beryllium was described and a patch test developed; a positive test at 72 hr was considered evidence of beryllium hypersensitivity and of CBD in patients with granulomatous lung disease (*17,18*). However, cutaneous hypersensitivity developed in 8 of 16 previously unexposed controls, and at least one fatality was associated with the patch test (*19*). The patch test was never widely used and is rarely used today because of safety concerns and the test's proven ability to induce hypersensitivity.

Two *in vitro* tests have been developed to test for hypersensitivity to beryllium: the migratory inhibitory factor (MIF) test and the lymphocyte proliferation test (LPT). MIF is secreted by activated T lymphocytes during antigenic stimulation to keep macrophages from migrating. In theory, identifying hypersensitive people by incubating lymphocytes from the blood or bronchoalveolar fluid with beryllium and testing for MIF should be possible. In practice, this test is technically difficult and gives results that are both insensitive (even to well-established CBD) and difficult to reproduce (*20*). The MIF test is no longer used.

The current test for beryllium hypersensitivity is the LPT (*20*). In the LPT, lymphocytes are taken from the peripheral blood or from bronchoalveolar fluid (*21*) and exposed *in vitro* to beryllium sulfate. If the patient is hypersensitive, T lymphocytes will proliferate. Typically, a stimulation index is determined by comparing proliferation among lymphocytes incubated with and without beryllium sulfate.

Rossman et al. (*22*) looked at the sensitivity and specificity of the LPT in a small series of cases and controls; bronchoalveolar lymphocytes were exposed *in vitro* to beryllium sulfate; a positive proliferative response was defined as a stimulation index greater than 5 on two separate determinations. The 23 beryllium workers evaluated in the study included 14 patients who clearly met the registry case definition for CBD (described above). For these 14 patients, the sensitivity of the proliferation test was 100%. The 22 controls selected included 16 patients with sarcoidosis and 6 normal volunteers; none of the controls had positive proliferative tests (100% specificity for these 22 controls). When the proliferation tests were repeated with lymphocytes from peripheral blood, the sensitivity for CBD was lower.

Kreiss et al. (*23*) demonstrated the utility of screening the peripheral blood of exposed workers using the LPT. The test identified several new cases of CBD among nuclear workers and in the ceramics industry (*24,25*). The "predictive value positive" of a confirmed test in the ceramics workers was 100%, but two cases of CBD initially identified by chest X ray did not have consistently abnormal blood tests. In other words, while a positive blood test can confirm CBD, a negative blood test (alone) does not exclude it.

Genetics of CBD. CBD is an immune hypersensitivity disorder caused by an interaction between beryllium and sensitized helper ($CD4^+$) T lymphocytes. For this interaction to occur, the small beryllium molecules must first be bound to a carrier protein. The antigen (a beryllium/protein complex) is then processed and presented to T lymphocytes by a major histocompatibility complex Class II molecule. This molecule consists of an α-chain and a β-chain that interact to bind the antigen. Because the substitution of a single amino acid can determine what antigen is bound, Richeldi et al. (*26*) recently studied the genes that encode the β-chain in 33 cases (exposed workers with CBD) and 44 controls (exposed workers without CBD). These researchers found that 97% (32/33) of the cases exhibited the amino acid glutamate (rather than lysine) at position 69 of a cell-surface glycoprotein involved in antigen recognition. This marker (Glu^{69}) was present in only 30% (13/44) of the controls, suggesting a significant genetic role in the immune process leading to CBD. This finding could have relevance for counseling in certain occupational settings (*26*).

Differential Diagnosis of CBD

The known causes of granulomatous disease (with examples in parentheses) are bacterial (brucellosis, leprosy, salmonellosis, and tuberculosis), fungal (blastomycosis, coccidiomycosis, and histoplasmosis), viral (cat scratch fever and lymphogranuloma venereum), helminthic (schistosomiasis, trichinosis, filariasis, and capillariasis), or metallic (beryllium and zirconium). The causes of some granulomatous diseases (sarcoidosis, Crohn's disease, and Wegener's granulomatosis) are unknown (*27*). Sarcoidosis is the granulomatous disease that is clinically the most similar to CBD. A careful occupational and environmental history can be helpful, but even well-documented exposure to beryllium does not eliminate the possibility of sarcoidosis. Clinical findings that are (when present) more characteristic of sarcoidosis include extensive hilar adenopathy, spontaneous remission, and the presence of extrapulmonary manifestations (e.g., erythema nodosum, parotid involvement, bone changes). Certain findings (variably present in sarcoidosis) have never been reported in a patient with CBD, including uveitis, uveoparotid fever, cranial or peripheral nerve involvement, and cystic bone lesions.

None of these clinical features is adequately sensitive or specific to reliably distinguish between sarcoidosis and CBD in individual patients. Though not part of the original beryllium registry case definition, the LPT is extremely useful in identifying individuals who have developed beryllium hypersensitivity. Most notably, the LPT was used to identify a cluster of CBD in a metal refinery after one worker questioned the diagnosis of sarcoidosis given to him and several co-workers (*6*). This test is now available at a handful of medical centers in the United States.

A number of medical tests (other than the LPT) are also useful in the quest to identify the cause of a patient's granulomatous pulmonary disease and assess the physiologic impact of the disease. The tests selected to evaluate a new patient would typically include 1) measurement of angiotensin-converting enzyme, a nonspecific marker of disease activity; 2) chest radiograph to assess the extent of chest disease; 3) immune parameters and lymphocyte proliferative responses to assess the immune system and test for hypersensitivity to beryllium; 4) liver function tests to assess liver involvement; 5) review of biopsy slides for evidence of infection, malignancy, suppurative processes, and

granulomatous processes; and 6) cultures and microscopic examination of bronchoalveolar lavage (BAL) fluid for evidence of infection, malignancy, or hypersensitivity.

Summary

CBD has historically been a difficult diagnosis to make with certainty; the diagnosis has typically required physicians to document beryllium exposure by history or by demonstrating excess beryllium in biologic specimens, and to meet certain clinical and pathologic criteria for chronic granulomatous pulmonary disease, criteria that are also present in other granulomatous diseases such as sarcoidosis.

In routine medical practice, the lack of a known (typically occupational) exposure has usually precluded active consideration of CBD in patients with granulomatous disease. If no other etiology is found, sarcoidosis has been the diagnosis of exclusion. This approach has rested upon unstated assumptions that 1) the only significant exposures are occupational; 2) the worker and employer know about the exposure; 3) the exposure is disclosed to the physician; and 4) the physician understands the clinical implications of beryllium exposure.

The validity of these assumptions has not been tested, and in some recent cases it is demonstrably false. When the clinical findings are consistent with granulomatous disease, CBD can now be diagnosed (or excluded) by assessing the immune response to beryllium (*28*). This specialized testing requires *a priori* coordination with an appropriate laboratory.

The best time to consider CBD is during the initial evaluation of patients with granulomatous pulmonary disease because a diagnostic bronchoscopy is usually performed. An LPT using BAL lymphocytes is the gold standard for diagnosing or excluding CBD; while a positive LPT using peripheral blood lymphocytes can also support the diagnosis, a negative test does not exclude it.

Recommendations

The state of the art for beryllium-related biomedical testing has advanced significantly, and reliable testing is available in a few centers. The following proposed guidelines are intended to encourage physicians to consider testing in the presence of uncertainty about the potential for beryllium exposure:

1. A careful environmental and occupational history should be taken on every new patient with granulomatous pulmonary disease.
2. If beryllium exposure is documented, T lymphocytes should be collected during the initial bronchoscopy for the LPT; it is also appropriate (but less sensitive) to test lymphocytes from peripheral blood for hypersensitivity to beryllium.
3. If beryllium exposure is not documented (but cannot be excluded), collection of T lymphocytes for the LPT should be considered during the initial bronchoscopy; it is also appropriate (but less sensitive) to test lymphocytes from peripheral blood for hypersensitivity to beryllium.
4. If beryllium exposure can be excluded with reasonable confidence, the patient is unlikely to benefit from beryllium-related biomedical testing.

(Testing for beryllium hypersensitivity requires *a priori* coordination with an appropriate laboratory; a listing of laboratories that perform the LPT is maintained by the Beryllium Support Group, P.O. Box 2021, Broomfield, CO 80038-2021 USA.)

To illustrate, a patient who once worked at or lived by a foundry processing metals from a variety of sources may have beryllium exposure that has not been documented; thus, some uncertainty remains and testing can reasonably be considered.

Uncertainties about beryllium exposure can also be affected by a physician's knowledge of industry; two physicians might appropriately make different decisions about testing in similar situations. The following points are offered to support the consideration of testing when the patient's potential for exposure is uncertain: 1) chronic granulomatous disease is potentially a life-threatening condition; 2) management decisions and prognosis are clarified by recognizing CBD; 3) the diagnostic test (LPT) is very specific for beryllium hypersensitivity when performed by an experienced laboratory; 4) exposure and disease can be widely separated in time and location; 5) exposure histories are not always reliable; and 6) a case of CBD can have public health significance as a sentinel case.

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