Chronic beryllium disease

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Abstract

Chronic beryllium disease (CBD) also know as berylliosis is an occupational hypersensitivity disorder caused by beryllium exposure at the workplace. It is characterised by non-caseating, non-necrotising granulomata within affected organs, most frequently lung and skin. The main symptoms include dry coughing, fatigue, weight loss, chest pain, and increasing shortness of breath. Inhalation of beryllium dust or fumes and dermal contact with beryllium and its compounds represent the primary ways of human beryllium uptake. Acute berylliosis is now extremely rare. Since CBD is a perfect phenocopy of sarcoidosis, the differential diagnosis relies both on occupational history giving evidence for beryllium exposure and tests demonstrating beryllium sensitisation (beryllium lymphocyte proliferation test). Genetic predisposition seems to play an important role in CBD development. The diagnosis is based on the association of beryllium exposure and sensitisation with symptomatic disease including abnormal lung function and chest radiographs. Progressing disease is treated with corticosteroids. Close monitoring of symptoms and follow-up pulmonary function testing is recommended for all individuals with suspected CBD.

Key words

chronic beryllium disease, acute beryllium disease, berylliosis, beryllium, granulomatous disorders, occupational lung disease.

Disease name and synonyms

Chronic beryllium disease - Chronic beryllium lung disease – Berylliosis - Beryllium granulomatosis - Beryllium pneumonosis

Definition

Chronic beryllium disease (CBD) is an occupational hypersensitivity disorder caused by beryllium exposure at the workplace. It is characterised by non-caseating, non-necrotising granulomata within the affected organs, most frequently lung and skin.

Introduction

Beryllium, which was discovered in 1798 by the French chemist Nicolas Louis Vauquelin, is the fourth element in the periodic table. It has an atomic weight of nine and is the second lightest metal known. As a result of its several advantageous properties, beryllium and its alloys have found widespread use in industry. Beryllium's toxicity was first identified in the 1930s, and later, in 1950s the beryllium's toxicity was officially recognised as environmental and occupational hazard, and control measures for preventing contamination were established. Due to these measures the acute berylliosis is now extremely rare in the Western world. Chronic berylliosis, however, continues to occur in individuals exposed to beryllium at the workplace. Being a perfect phenocopy of sarcoidosis, CBD is rarely diagnosed [1].

Occupational and environmental beryllium exposure

Copper-beryllium alloys withstand high temperatures and mechanical stress; they are extraordinarily hard but flexible, resistant to corrosion, do not spark, and are nonmagnetic. Beryllium and its alloys share a number of properties with aluminium, which explains their frequent use in aerospace and defence industry. Because the addition of beryllium improves the electrical and thermal conductivity of alloys, this metal is frequently used also in electronic and microelectronic applications such as semiconductor devices and integrated circuits requiring heat dissipation. Springs, switches, relays, and connectors in computers, radar, automobiles, telecommunication equipment, tools, and other instruments contain beryllium. Copper-beryllium is a common substrate of gold plated electrical connectors. Copper-beryllium scrap is often mingled with copper scrap for recycling. As a result, workers in both metal recycling and precious metal recovery industries encounter beryllium.

Beryllium is used in casting of many different alloys where it refines the grain size resulting in better surface polishing, reduces melt losses, and improves casting fluidity. It is also used as acid catalyst in organic reactions, and as an additive to glass and plastics. Neutron moderators or reflectors in nuclear reactors and X-ray windows also contain beryllium. It is frequently found in gems and, depending on work processes, gem polishers are exposed. Jewellers may be exposed when precious stones are framed or polished. Since optical crystals contain beryllium, the beryllium-exposure takes place in the production of precision optical instruments including fiberoptics.

Beryllium oxide is the most important high-purity commercial beryllium chemical, with primary use in ceramics manufacturing. Because beryllium-oxide is transparent to microwaves, it is also used in microwave devices.

Thus, the workers potentially exposed to beryllium are beryllium ore miners, beryllium alloy fabricators, phosphor manufacturers, ceramic workers, missile technicians, nuclear reactor workers, electric, electronic, and optical equipment workers, and jewellers. Notably, workers in downstream industries and crafts using beryllium-containing parts may be exposed. Previous exposure may still lead to disease, for example, in workers who were involved in the manufacture of fluorescent powder and in the manufacture and salvage of fluorescent lamps. A relatively new working environment with a risk of beryllium exposure is the recycling of

electronic parts. Due to the expanding use and applications of beryllium and its alloys, exposure can occur in environments other than the traditional areas of beryllium manufacturing. Work environments associated with potential exposure are listed in Table 1.

Table 1. Workplaces and products with potential beryllium-exposure

- Additives to glass, ceramic, plastics - Aerospace industries (*e.g.* aircraft frames, engines, and brakes) - Automobile industries (engines, electronic parts) - Brass alloys - Camera shutters - Ceramic industries - Chemical industries - Dental workshops - Electrical relays - Electronic industries - Fluorescent lamp production/disposal - Gems	- Golf clubs - Gyroscopes - Metallurgic industries/recycling - Microelectronics - Microwave devices - Military vehicle armour - Mirrors - Missile production and maintenance - Missile guidance systems - Non-sparking tools - Nuclear reactors and industries - Optical industries/workshops	- Pen clips - Personal computers - Precision instruments - Recycling workplaces - Satellites - Springs - Structural material in space technology - Submarine cable housings - Transistor mountings - Wheels - X-ray tubes

Certain fossil fuels such as coal and oil contain beryllium-compounds purported to account for the presence of beryllium in some community air samples and tissues of city residents. Municipal waste combustion is another source of beryllium-emission.

In low concentrations beryllium occurs naturally in rocks, soil, volcanic dust, and minerals. Although trace amounts of beryllium can be found in drinking water, food, and tobacco, food is not considered a significant source of human beryllium-exposure and there is no evidence that beryllium is moving from soils into food or feed plants in amounts detrimental to health. Inhalation of beryllium dust or fumes and dermal contact with beryllium and its compounds represent the primary ways of human beryllium uptake. Since CBD can take up to as many as 40 years to appear, discovering the origin of the disease onset can be difficult.

Exposure standards

There are no international exposure standards. Daily-weighted average (DWA) estimates of exposure of 0.02 mg/m^3 were found safe [2]. This standard is accepted by the Environmental Protection Agency Integrated Risk Information System Reference Concentration of the United States of America (USA) [3]. It represents the mean ambient air level that should not be exceeded in any 24-hour day. Time-weighted average (TWA) values for occupational 8-hour exposure differ from country to country. An occupational study showed that exposure with TWA values of 0.02 mg/m^3 does not provoke adverse effects [4]. However, the Occupational Health and Safety Administration (OSHA) of the USA has set the Permissible Exposure Limit (PEL) at 2.0 µg/m^3. It has been recognized that even TWA level of 0.02 mg/m^3 is not completely safe [4] (probably related to the hypersensitivity nature of the disease). For physicians, it is crucial to know that the dose response to beryllium is not linear. Unlike the classic pneumoconiosis, high dose exposure is not required to trigger CBD. Virtually, all epidemiological series report cases of CBD in individuals with trivial-seeming exposure: security guards, administrative and secretarial staff. In addition, disease has been reported in community cases, so called “neighbourhood”

cases (people not employed by a beryllium using company but exposed to smokestack emissions of the toxic dust), as well as in spouses of beryllium workers.

Aetiology

In 1951, it was demonstrated that patients with beryllium disease developed a delayed-type cutaneous response to beryllium salts [5]. Peripheral blood and bronchoalveolar (BAL) lavage mononuclear cells of patients with beryllium disease proliferate *in vitro* in response to beryllium challenge, demonstrating the immunologic hypersensitivity nature of CBD. Cells from healthy controls or patients with other granulomatous disorders do not proliferate in the presence of beryllium. Thus, this reaction can be used to identify beryllium hypersensitivity. Furthermore, it was demonstrated that beryllium-specific T-cell lines and clones exhibited a dose-dependent Major Histocompatibility Complex (MHC) class II-restricted proliferation in response to beryllium, but did not respond to recall antigens or to other metals; in addition, all beryllium-specific clones studied had different rearrangements of T-cell antigen receptors [6-7]. It was concluded that CBD is a hypersensitivity disease in which beryllium plays role of specific antigen. The susceptibility to acquire CBD is linked to the individual genetic background. The presence of HLA-DPB1 (major histocompatibility complex, class II, DP beta 1) alleles positive for glutamate at position 69 is the most powerful genetic risk factor known [8]. It has yet to be determined whether this risk is due to any or only certain glutamate 69-positive alleles or allele combinations [9-10]. In addition, the genetic markers associated with disease susceptibility and the exposure dose have been identified as independent risk factors [11]. This suggests the existence of complex gene environment interactions [12] with different genetic background responsible for the susceptibility for CBD [13].

Clinical description

Acute disease

Acute berylliosis is caused by high dose beryllium exposure and shares clinical characteristics with acute sarcoidosis. Patients develop dose-dependent diffuse interstitial infiltrates, dyspnea, fatigue, fever, night sweats, and cough. The onset is usually immediate but may be delayed for up to 3 days. Pulmonary function tests reveal obstructive and/or restrictive lung disease with impaired gas exchange. Biopsy specimens of the lung show a lymphocytic interstitial pneumonitis indistinguishable from chemical pneumonitis due to other causes. Approximately one third of the acute cases progress to chronic [14]. Although the acute disease is mainly of historical interest, sporadic cases are still reported [15].

Similarly to acute and chronic hypersensitivity pneumonitis or sarcoidosis, acute berylliosis may represent an acute form of an hypersensitivity response. In this case, it represents one end of the inflammatory response spectrum, with the chronic form, CBD, representing the other. The pathophysiological factor(s) responsible for the switch from acute to chronic remains to be defined.

Chronic disease

A number of metals can cause diseases mimicking sarcoidosis, the most prominent being beryllium [16]. A wide spectrum of morbidity exists with CBD. Some patients may be completely asymptomatic while others may progress to disabling lung dysfunction and death. The factors that determine progression of the disease are not clear. Beryllium commonly produces granulomas in the lungs and, in some cases, also in the liver, spleen, and myocardium. In addition, it can cause skin nodules, contact dermatitis, and poor wound healing. The chronic form of beryllium lung disease develops insidiously with symptoms of dyspnea on exertion, cough, fatigue, chest pain, weight loss, night sweats, fever, and anorexia. In rare cases liver,

spleen, myocardium, skeletal muscles, salivary gland, and bony involvement may imitate a systemic chronic inflammatory disease. The link between this granulomatous disorder and beryllium exposure can be elusive because the latency from time of the first beryllium exposure to the development of clinical disease ranges from a few months to several decades; dose- and time-exposure may be minimal [17-18]. Chest radiographs range from small nodular opacities with an upper level predominance to formation of conglomerate masses or can be normal. Since the high-resolution computed tomography and pulmonary function tests in patients with granulomatous lung disease can be normal, the diagnosis CBD should not be excluded on the basis of those negative results [19]. Mediastinal and hilar lymphadenopathy is present in approximately one third of the individuals examined by chest radiograph or computed tomography. In the early stages of the disease, alterations in lung function include airflow obstruction, later developing a mixed pattern of obstruction and restriction, or pure restriction toward the end stage of the disease. Gas exchange abnormalities are particularly notable, especially during exercise.

The histopathology includes a combination of mononuclear cell infiltration and typical non-caseating granulomas with varying degrees of fibrosis [20]. The pulmonary histological appearance is indistinguishable from that of sarcoidosis. Demonstration of beryllium within the granulomas may confirm the diagnosis. However, the absence of beryllium in tissue analysis does not exclude the diagnosis, especially in the light of the hypersensitivity nature of CBD and the fact that biorelevant tissue concentrations are below the detection limits [21-22].

Based on CBD registry data from the USA, 1972, approximately 25% of patients die of this disorder [23]. Early diagnosis and termination of beryllium exposure seems to diminish this number.

Diagnostic criteria and differential diagnosis

The diagnosis of berylliosis is decisive when a non-caseating granulomatous disease (otherwise diagnosed as sarcoidosis) is accompanied by documented occupational (or in rare cases ambient) beryllium exposure in combination with beryllium hypersensitivity.

Beryllium hypersensitivity is identified by beryllium lymphocyte proliferation test (BeLPT) in peripheral blood or bronchoalveolar lavage. BeLPT demonstrates a beryllium-specific immune response. It confirms the diagnosis of CBD and excludes sarcoidosis. Skin tests such as patch test or intracutaneous tests can be used [23-24] but are generally not accepted when the diagnosis CBD is of legal, occupational, or social consequences. In theory, the skin tests may induce sensitisation, so they are not advisable in people with ongoing exposure. It has to be noted that granulomatous disease is not mandatory for diagnosis of CBD. Mononuclear alveolitis in the presence of beryllium exposure and hypersensitivity in combination with symptomatic disease is sufficient to support the diagnosis. This is why some authors suggest, for practical reasons, to omit histopathologic criteria [25]. Many different criteria are used to define CBD. They reflect the changes in our understanding of the disease pathophysiology and the availability of diagnostic tests. Other differences may be related to the purpose of making the diagnosis such as clinical care, surveillance, research, or compensation.

The sensitivity of BeLPT is under debate. Reported sensitivity ranges between 38% [26] and 100% [27] with low inter-laboratory reproducibility [28]. Consequently, there will be cases of berylliosis that will not be diagnosed due to false negative test results. Thus, in cases with negative BeLPT results and doubtless exposure, the tentative diagnosis of CBD has to be either excluded or verified with multiple independent tests. The BeLPT-specificity for CBD is generally accepted since positive tests have not been reported in non-exposed controls or patients suffering from other granulomatous disorders [24,26,27,29]. Its positive predictive value is comparable to other accepted medical tests with sensitivity of 0.683, specificity of 0.969, and positive predictive value of one abnormal test of 0,253 [30]. In case of any doubt, the test should be repeated with cells from bronchoalveolar lavage. This test is considered as more sensitive

because of the higher proliferation capacity of bronchoalveolar lymphocytes in response to beryllium [31]. This enhanced responsiveness can be markedly reduced by the effect of cigarette smoking. At present, BeLPT remains the only standard diagnostic test reflecting etiologic criteria.

Not every individual with a positive BeLPT suffers from CBD [17]. Some beryllium-exposed individuals have repeatedly positive results demonstrating sensitisation without pulmonary granulomas or other signs of disease. In a follow-up study, 31% of those individuals progressed to symptomatic CBD within four years [32]. It is still a matter of debate whether asymptomatic patients without pulmonary function defects but with positive BeLPT and granuloma have early disease.

The above-mentioned limits of background proliferation are laboratory-dependent and need to be individually established using mononuclear cells of unexposed controls. The mean plus two standard deviations is usually taken for the upper limit. To obtain a reliable value, multiple cell cultures should be performed, at least twelve in parallel. Cell cultures with different concentrations of BeSO4 ranging from 10^{-4} to 10^{-6} mol/L are run in quadruplicate; the proliferation is estimated once or several times between 3 and 8 days of culture. Tests with at least two elevated proliferation values are considered abnormal. Mitogen-induced proliferation serves as a non-specific control [26-27]. It has to be noted that this test is not standardised and some laboratories use absolute numbers of stimulation indices as threshold or request dose-dependent proliferation for positive tests. As a consequence, the clinician has to evaluate whether the results of the test support or invalidate a tentative diagnosis of CBD. Cell culture details should be reported by the laboratory for correct interpretation of the results. Since a specific positive control is not available, some authors demand two independent tests to accept the clinical consequence [30]. Test specification released by the Department of Energy of the USA in 2001 (Specification 1142-2001) to standardise BeLPT for epidemiological purposes can be used as a guideline to evaluate or to validate the test. Measuring beryllium in urine and tissue samples may unequivocally identify the exposure, however, concentrations of biological relevance are far below the sensitivity of the routine tests, thus limiting the clinical value of negative results [21-22,33,34,35].

The known causes of granulomatous disease are bacterial, fungal and viral infections, helminths, or metalls. However, some other granulomatous diseases have unknown causes and should be considered for differential diagnosis (a selected list is given in Table 2).

Table 2. Differential diagnosis of granulomatous disorders

Cause of granuloma formation	**Disease**
Bacterial	Brucellosis, B*artonella henselae* (cat scratch fever), chlamydia (Lymphgranuloma venereum), leprosy, salmonellosis, tuberculosis
Fungal	Blastomycosis, coccidiomycosis, histoplasmosis
Viral	Measles virus
Helminthic	Filariasis, schistosomiasis, trichinosis
Metallic	Aluminium, beryllium, titanium, zirconium
Bioaerosols	Hypersensitivity pneumonitis (*Rectivirgula faeni*, *Trichosporon cutaneum*)
Drugs	Allopurinol alveolitis
Unknown	Crohn's disease, Wegener disease, sarcoidosis

Certain clinical findings are more characteristic for sarcoidosis, *e.g.* extensive hilar adenopathy in the absence of parenchymal infiltrates (radiographic Type I of sarcoidosis) and spontaneous resolution. Others have never or only rarely been reported in berylliosis, *e.g.* cystic bone lesions and cranial or peripheral nerve involvement. None of these clinical features, however, is adequately sensitive or specific to distinguish reliably sarcoidosis from berylliosis.

Disease monitoring and therapy

Prevention is a key component in the management of CBD. Elimination of exposure and continual education of individuals using beryllium products remain essential for prevention of the disorder. An occupational study reported reversibility of the functional and radiographic defects with reduction or termination of the exposure [36]. Although there are no studies demonstrating unequivocally a benefit of this step, it is recommended for all CBD patients. The social implications of this measure in sensitised individuals should be justified on individual basis, in combination with genetic counselling [37].

Patients with early disease (*i.e.* sensitisation in combination with granuloma but without symptoms or lung function defects) should be regularly monitored (routine lung function tests, exercise physiology, and chest radiographs) to detect progressive disease. Serological markers of disease activity used in sarcoidosis, such as angiotensin converting enzyme, soluble interleukin-2 receptor or neopterin, can be used to gauge the inflammatory activity of CBD [38-39]. However, treatment decisions are made on the basis of symptoms and progression of organs dysfunction. Screening workers who are exposed to beryllium fumes or dust or who develop an allergic reaction to these substances is an effective way to control symptoms and prevent disease progression.

Progressive disease is indicated for corticosteroid therapy. Systemic corticosteroids are the mainstay of CBD treatment. Drug regimens established for sarcoidosis are used. Starting doses of prednisolone 0.5 to 0.8 mg/kg body weight/day are recommended. The response to corticosteroids in CBD is quite variable. Stabilisation or improvement takes place in most patients. However, under dose tapering or after therapy cessation some patients relapse; in these cases a long-lasting maintenance therapy may be needed. Long-lasting remissions and recalcitrant disease have been reported [40]. There is no systematic studies of the use of other immunosuppressive, immunomodulatory or anti-inflammatory drugs in CBD. For patients who either do not respond to high doses of prednisolone or require unacceptably high maintenance doses, a second-line therapy with corticosteroid-sparing regimens (used also in sarcoidosis) should be advised: methotrexate, azathioprine, cyclophosphamide, hydroxychloroquine, cyclosporine [41-42]. Relatively few patients progress to end-stage lung disease. In end-stage cases, lung transplantation may be considered.

A significant excess mortality from lung cancer was found by a cohort of CBD patients and beryllium-exposed workers without CBD, providing the first evidence for the carcinogenicity of beryllium [43]. The risk of lung cancer was found greater in CBD patients than in exposed to beryllium workers [44-45]. On the basis of epidemiological data and animal studies, beryllium is considered a human carcinogen. Despite the variations in the national guidelines and legal implications, special attention to signs of lung cancer should be paid in follow-up examinations.

Prevalence and prevention

It is estimated that, depending on exposure type and intensity, 1% to 20% of exposed individuals develop CBD. The overall prevalence among individuals who have worked under beryllium-exposure ranges from about 1% to 5%. Among beryllium workers routinely engaged in certain work tasks such as machining and ceramics dry pressing, CBD prevalence is as high as 10% - 20% [2,29]. Considering that CBD is a hypersensitivity disorder, the beryllium dose sufficient to cause or to perpetuate disease is difficult to establish. Screening programs have

found a 10-fold higher prevalence of beryllium sensitisation than that of CBD [17]. Moreover, sensitised individuals may progress to symptomatic CBD even after exposure ceases [23,32] thus confirming the necessity of continuous monitoring of sensitised individuals during and after beryllium exposure.

Because of the hypersensitive nature of CBD, industrial hygiene measures cannot assure complete eradication of potential beryllium exposure. On the other hand, mandatory exclusion of individuals positive for certain genetic markers from workplaces with potential beryllium exposure is not practical, since the predictive value of the known markers is not sufficient to enable an ethically sound verdict. Although no proof confirms the benefit of exposure cessation (improvement of the disease course or delayed progression), advising all patients with CBD to avoid any further exposure to beryllium is prudent. Voluntary counselling of sensitised workers is a cost-effective way of preventing CBD, although social, ethical and legal implications may prevent its implementation [37].

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