Diagnoses of Chronic Beryllium Disease within Cohorts of Sarcoidosis Patients*

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Abstract

Background: An increase in chronic beryllium disease has been suggested due to higher industrial use of beryllium-alloys. Since occupational chronic beryllium disease is a perfect phenocopy of sarcoidosis it might be misdiagnosed as sarcoidosis.

Objective: We hypothesize that chronic beryllium disease exists in cohorts of sarcoidosis patients.

Methods: In a prospective case collection sarcoidosis patients were evaluated for potential beryllium exposure. In those patients in whom beryllium exposure was confirmed and beryllium hypersensitivity demonstrated the diagnosis sarcoidosis was rejected and corrected to chronic beryllium disease.

Results: In 84 patients seen for reevaluating or making the diagnosis of sarcoidosis beryllium exposure was recognized and the diagnosis chronic beryllium disease was made in 34/84 patients. The time lag between clinical diagnosis of sarcoidosis and the final diagnosis of chronic beryllium disease ranged from 0 to 18 years (median: 3 years) and the mean age at time of diagnosis of chronic beryllium disease was 43.9 years (range: 25 to 80 years). beryllium-contaminated workplaces causing disease encompassed a wide spectrum of industries and technical trades in which beryllium-exposure is generally not perceived as a health hazard.

Conclusion: Chronic beryllium disease still belongs to the spectrum of differential diagnoses of granulomatous disorders.

Keywords:

chronic beryllium disease; sarcoidosis; diagnosis; lymphocyte proliferation test

<u>Abbrevations</u>:

BeLPT: beryllium-lymphocyte proliferation test

BrdU: Bromo-desoxyuridine

CBD: Chronic Beryllium Disease

ConA: Concavalin A

PHA: Phythemagglutinin

HLA-DPB: Human leukocyte antigen-DP beta chain

Introduction

Chronic beryllium disease (CBD) is an occupational hypersensitivity disorder elicited by beryllium exposure at the workplace. It is characterized by non-caseating granuloma within affected organs, predominantly lung and skin [1]. Due to their attractive characteristics Copper, Aluminum, Nickel, Magnesium, and Iron alloys containing beryllium are increasingly used in various industries and trades [2, 3]. Historically, the defense, nuclear, and aerospace sectors have been the largest users of beryllium-containing alloys. Meanwhile, however, more than 50 % of the annual beryllium consumption of the USA of 200 metric tons is distributed to the computer and electronic industries [4]. A similar percentage can be assumed for other industrialized nations. As a consequence of the increasing use of beryllium, it is estimated that the number of exposed workers in the USA has risen from 30,000 in the 1970s to 200,000 or even 800,000 in 2000. Moreover, 4,000 to 16,000 undiagnosed cases of chronic beryllium disease may exist in the USA alone [5]. In this context, it is remarkable that chronic beryllium disease is only rarely diagnosed. Since it is a perfect phenocopy of sarcoidosis, its differential diagnosis relies on occupational history giving evidence for beryllium exposure and tests demonstrating beryllium sensitization [6, 7]. For the latter routine tests are available only at a few specialized centers which leads to the assumption that unrecognized chronic beryllium disease arising outside the classical beryllium worker populations may be misdiagnosed as sarcoidosis [4, 8, 9]. In the past, several groups including ours reported on the diagnosis of chronic beryllium disease made in the diagnostic work-up of "sarcoidosis patients" [8-10]. Therefore, we included chronic beryllium disease in the differential diagnostic spectrum routinely checked when making the diagnosis of sarcoidosis.

To this end, we took a detailed occupational history of all patients of one tertiary referral center in Germany and one in Israel where sarcoidosis was either diagnosed for the first time or reevaluated. In addition, we established the beryllium-lymphocyte proliferation test (BeLPT) in our institutions for routine use. Based on published data we asked for workplaces and work processes known to be associated with beryllium-containing dusts, fumes, aerosols, or vapors and for potential by-stander exposure [2, 4, 11]. In cases with potential exposure, we performed BeLPT with peripheral blood mononuclear cells to check for beryllium sensitization [12]. After making the medical diagnosis of CBD based on positive BeLPT results and clinically assumed beryllium exposure, definitive diagnosis was established by an occupational evaluation of the workplace. Here we report on our experience on the differential diagnosis of CBD in a non-occupational, routine setting of apparent sarcoidosis in internal medicine clinics.

Materials and Methods

Patient Selection: From October 1997 to May 2005 patients with obvious or suspected occupational beryllium exposure referred for the clinical work-up of suspected sarcoidosis or CBD entered the study at the Medical Hospital, Research Centre Borstel, Borstel, Germany (from 1997 to 2001), the Department of Pneumology, University Medical Centre, Albert Ludwigs University, Freiburg, Germany (from 2002 to 2005), and the Department of Pulmonary and Allergic Diseases, Sourasky Medical Centre, Tel Aviv, Israel (1998 to 2005). To identify patients with possible beryllium exposure we compiled and up-dated a list of workplaces with exposure risk on the basis of the current literature [2, 11] and took a detailed occupational history from every sarcoidosis patients admitted to our centers using this list. The occupational settings in which we identified CBD cases are given in Table 2. In addition, we listed the following potential contacts during production or maintenance processes to be asked for in the occupational case history: microwave devices, transistor mountings, wheels, high-end sport devices (racing bicycles, golf clubs, etc), satellites, and electronic military guidance systems. However, none of our patients worked with an exposure risk in these additional settings. This approach resulted in a prospective case collection of 84 "sarcoidosis patients" with possible or known beryllium exposure. Demographic details and the contribution of the centers in Germany and Israel are shown in Table 1. Exposure was verified by consultation of the respective occupational medicine service and if necessary by a site visit through the respective legal authority.

Control Populations: 76 healthy employees of the involved institutions donated blood for BeLPT after an uneventful, routine occupational medicine examination including an occupational history asking specifically for circumstances with potential beryllium exposure. In addition, 31 sarcoidosis patients without corticosteroid treatment and no known beryllium exposure served as controls to demonstrate the specificity of the beryllium-lymphocyte proliferation test (Table 1). In

addition, 13 healthy colleagues of our patients with identical exposure pattern gave a blood sample for BeLPT (Table 1).

Beryllium-Lymphocyte Proliferation Test: All patients and controls of this study were free of systemic corticosteroid medication for at least six months prior to testing. A sample of venous blood was collected and mononuclear cells were prepared by gradient centrifugation. The BeLPT was initiated within 6 hours of venipuncture following established protocols [12-14] fulfilling the technical specifications of United States Department of Energy published in 2001 (Specification 1142-2001). Briefly, mononuclear cells were cultured at a density of 0.5×10^6 cells per ml either without any in-vitro stimulus (background and negative control, 32-fold), with 5 μg PHA per ml, 10 μg ConA (positive controls; 8-fold, respectively), or with $BeSO_4$ in concentrations ranging from 10^{-5} to 10^{-10} mol/L (8-fold each). After three days of culture ^{3}H-thymidine or Bromo-desoxyuridine (BrdU) was added to measure cell proliferation with established methods [12, 13, 15]. Both approaches are equivalent to that recently suggested by Frome et al. [16] including reference tests from healthy individuals.

Diagnostic Criteria of CBD: To establish the diagnosis of chronic beryllium disease the following criteria were used as suggested in the literature [1]:

1. Symptomatic disease with histological demonstration of non-caseating granuloma, pulmonary function impairment, and abnormal chest radiographs otherwise diagnosed as sarcoidosis,

2. proof of beryllium sensitization by two independently positive BeLPTs in the absence of any treatment with systemic corticosteroids for at least three months, and

3. proof of beryllium exposure. For the latter occupational safety experts of the relevant occupational health authorities evaluated the workplace.

In those cases with fulfilled criteria 2 and 3 but without criterion 1 beryllium sensitization was diagnosed [1, 17].

Results

Over a period of 7 years patients for whom the diagnosis sarcoidosis was suspected or re-evaluated, a potential beryllium exposure was recognized in 84 individuals. Consecutive BeLPT and positive verification of beryllium exposure established the diagnosis of chronic beryllium disease in 34 patients (Table 1). In all but six of these cases of chronic beryllium disease the diagnosis of sarcoidosis was initially made and there was an average delay of 4 years (median: 3, range: 0.25 - 18) before reevaluation established the diagnosis of chronic beryllium disease. The age of the patients at the time of CBD diagnosis was 43.9 years (range 25 to 80 years of age). In the aforementioned six cases (three in Israel and three in Germany) timely diagnoses of chronic beryllium disease were due to the alertness of primary physicians, occupational physicians, or pneumologists.

Although beryllium exposure could be demonstrated in the remaining 50 patients, due to reproducibly negative BeLPT findings using blood cells chronic beryllium disease was excluded and sarcoidosis confirmed. Thirteen exposed healthy colleagues of our patients could be recruited for BeLPT and seven of them exhibited sensitization without evidence of chronic beryllium disease. Seventy-six healthy individuals without known beryllium exposure served as controls and all exhibited negative BeLPT results (Table 1). Another control cohort consisted of 31 sarcoidosis patients without known beryllium exposure. In none of these individuals a beryllium sensitization could be detected by BeLPT, which demonstrates its specificity.

The workplaces where beryllium exposure was identified are listed in Table 2. In our study on German and Israeli cohorts, dental laboratories are the leading occupational setting of beryllium exposure. However, as already recognized by others we also observed a wide spectrum of

workplaces with beryllium exposure ranging from high tech industries to technical trades (Table 2).

Discussion

Our differential diagnostic approach demonstrates that cases of chronic beryllium disease may be misclassified as sarcoidosis, which stresses the necessity of detailed occupational history and eventually BeLPT within the repertoire of diagnostic tools [3, 6, 7, 10]. A correct diagnosis is of utmost importance since cases of chronic corticosteroid-resistant sarcoidosis may in reality be chronic beryllium disease cases with ongoing exposure, which might prevent response to therapy or spontaneous resolution. The natural courses of chronic beryllium disease and beryllium sensitization are not analyzed in detail. However, in general the prognosis is not as good as for sarcoidosis with an estimated mortality of up to 25% [6]. However, recent estimates do not exist. Depending on exposure dosage 2 - 20% of exposed individuals become sensitized. 40 – 60% of sensitized individuals develop granuloma without symptomatic disease and of these about 50% - 100% progress to symptomatic chronic beryllium disease [5, 18, 19]. Progression to clinical disease seems to depend on exposure type [20]. Whether termination of exposure is mandatory to prevent progression is not known but theoretical scenarios with risk estimation based on occupational epidemiology suggest a benefit from beryllium avoidance [21]. In addition, retrospective studies showed that chronic beryllium disease improved or even resolved with reduction or termination of exposure [22, 23]. In one of our patients we could observe the same phenomenon; chronic beryllium disease came to a spontaneous resolution after a change to a beryllium exposure free workplace. Thus, after establishing the diagnosis of chronic beryllium disease avoidance of beryllium is the first recommended therapeutical measure [24].

Occupational history is the mainstay to reveal evidence for possible beryllium exposure and it is not substitutable by determination of beryllium concentration in tissue or urine. Elevated levels unequivocally demonstrate exposure; however, normal values have been observed in clear-cut

cases of chronic beryllium disease [25] and even in a fatal case after short term exposure [26]. In chronic beryllium disease HLA-DPB alleles encoding for glutamate at position 69 (Glu69 positive) are overrepresented [27] and genotyping has been suggested as a diagnostic or screening tool. However, the high frequencies of Glu69 positive HLA-DPB alleles of about 33 % in healthy Caucasian, 40 % in African- American and up to 59 % in Chinese populations result in low positive predictive values and low specificity for genotyping at the observed disease prevalence [28]. In addition, other polymorphic genes outside the major histocompatibility complex also contribute to susceptibility and disease manifestation [29, 30]. Thus, the presence of Glu69 positive HLA-DPB alleles can only serve as a marker for the risk of sensitization and not as a diagnostic criterion (2). An extended genetic testing for supratypic markers, as suggested for HLA-DRPheβ47, might give additional information on the risk of beryllium-sensitization [31], however, a high frequency of this named marker in sarcoidosis [21, 32] makes it unlikely that this approach will improve diagnosis of CBD in the near future.

Due to the increased use of beryllium an increase in the incidence and prevalence of chronic beryllium disease is expected in industries using or manufacturing parts with beryllium-alloys or beryllium-ceramics and the fact that it has been diagnosed outside the classical beryllium worker sector supports this notion [2, 4, 5]. Our binational study demonstrates that relevant beryllium exposure followed by sensitization and eventually chronic beryllium disease exists in a wide spectrum of workplaces in different industries and trades other than the classical workplaces with beryllium exposure known from US-studies (Table 2). Inhalable particulate matter or fumes from any beryllium-containing material can be generated by high temperatures or by physical processes such as grating, grinding, scraping, lapping, and cutting. Less adherent oxides and hydroxides formed at high temperatures may lead to dust exposure [4], which might also use the skin as a route to cause sensitization [33]. Moreover, beryllium carried on shoes, clothing, and

skin from the workplace might cause exposure with consecutive sensitization for individuals at workplaces without generation of beryllium dust [34] or even at home [10]. Thus, potentially hazardous workplaces due to beryllium exposure are ubiquitous in our industrialized world and chronic beryllium disease has to be taken into account whenever a disease with non-caseating granulomata is under scrutiny. BeLPT is the sole diagnostic tool to demonstrate sensitization, which is a prerequisite to make the differential diagnosis as demonstrated in our 34 cases of chronic beryllium disease. This number might even be an underestimation of chronic beryllium disease in our cohort since cases have been reported in which BeLPT with blood cells gave negative results and sensitization could only be demonstrated by BeLPT with cells of bronchoalveolar lavage [35]. A more frequent use of bronchoalveolar lavage cells might increase sensitivity since a higher frequency of beryllium-specific cells with a higher proliferative capacity is found in lung cells [35, 36]. Unfortunately, we could only make limited use of this option in our chronic beryllium disease-cases (data not shown).

In this context, the question arises whether false positive BeLPT results could cause an overestimation of the chronic beryllium disease outside the occupational setting. False positive results take place in a frequency of 0.00 to 3.35% and are identified by the fact that they cannot be confirmed by the mandatory repeated testing. This leads to a positive predictive value for the first abnormal test of 0.253 for chronic beryllium disease and of 0.580 for beryllium hypersensitivity [14]. False negative results have been reported in a range of 24 to 34 % depending on the used algorithms. For this reason two or more independent tests are requested by to exclude suspected beryllium hypersensitivity [14, 37]. In addition, methodological aspects of BeLPT have to be considered [12, 24]. One false positive initial test has been identified in our cohort by two consecutive negative BeLPTs, which lead to the diagnosis of sarcoidosis in a beryllium-exposed worker of a foundry. In a cohort of 291 unexposed new hires 3 abnormal tests

were observed and none of them could be repeated which leads to the conclusion that repeated testing is sufficient to exclude false diagnoses of beryllium hypersensitivity [14].

Only the diagnosis of chronic beryllium disease entails termination of beryllium exposure, which is, although not formally proven, the first recommended step of therapy. Moreover, seven sensitized healthy individuals could be identified who need thorough follow-up by occupational medicine since progression to chronic beryllium disease might take place [20]. Theoretical models suggest that residential exposure due to anthropogenic environmental contamination may lead to an incidental dermal pathway of beryllium uptake which may eventually cause sensitization [38], which leads to the hypothesis that non-occupational chronic beryllium disease might exist. However, the above mentioned large surveillance study does not support this notion [14].

The authors are aware that the data presented cannot be used to estimate chronic beryllium disease prevalence within sarcoidosis in Germany or Israel since our institutions are tertiary referral centers in which representative cross sections of sarcoidosis cohorts are not seen. In addition, some patients have been explicitly sent for performing BeLPT to establish or exclude the suspected diagnosis of chronic beryllium disease. The dimension of underdiagnosing sarcoidosis may be estimated by the fact that the 34 reported CBD cases have been found within a cohort of 536 sarcoidosis patients referred to the outpatient clinics of the involved institutions over the study period. In addition, a retrospective study of our center in Israel, not overlapping with the present one, detected 3 cases in a cohort of 47 reevaluated sarcoidosis patients [9], indicating a considerable number of misclassified cases. Diagnosing chronic beryllium disease is hampered by the phenomenon of a missing relationship between risk and dose or time of exposure [5]. Minimal exposure over a short period unrecognized by patient or physician may

cause disease decades later in life. A triggering co-factor has to be assumed but is not yet known. Thus, occupational history and eventually BeLPT remain the mainstay of diagnosing chronic beryllium disease. This test should be used more frequently since due to its hypersensitivity nature chronic beryllium disease is elicited by minimal beryllium exposures below occupational exposure limits and it cannot be completely eradicated by industrial safety measures [5, 17, 39]. Thus, it will be seen wherever and as long as beryllium is used and the fact that in about 40% (34 of 84) of "sarcoidosis patients" prescreened for beryllium exposure the diagnosis CBD was made suggests that the problem might be bigger than expected.

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Table 1

Results of beryllium-lymphocyte proliferation test (BeLPT) in beryllium exposed and unexposed

individuals

	n	Expo-sure	BeLPT *	Age (years ± SD)	Female / Male
Chronic Beryllium Disease	34 (22; 12)**	+	+	43.9±13.2	11/23
No exposure, no sensitization					
Healthy	76 (70; 6)	-	-	41.9±16.1	37/39
Sarcoidosis	31 (29; 2)	-	-	45.9±11.8	19/12
beryllium exposed groups without Chronic Beryllium Disease					
Healthy with Be sensitization	7 (7; 0)	+	+	48.9±12.5	1/6
Healthy without Be sensitization	6 (6; 0)	+	-	40.2±6.9	1/5
Sarcoidosis	50 (35 ; 15)	+	-	46.5±13.1	13/37

* Results are shown as positive (above individual cut-off) or negative proliferation response in

BeLPT, only reproducible positive results were accepted as positive; ** numbers in brackets

show number of patients in Germany and Israel, respectively. All patients and controls were free

of systemic corticosteroid therapy for at least six months prior to testing.

Table 2
Workplaces and occupational settings with beryllium exposure identified by occupational case history.

occupational beryllium exposure	CBD	Exposed sensitized healthy	Exposed non-sensitized healthy	Sarcoi-dosis exposed
Total number of individuals	34	7	6	50
Dental technician, dentist	13 (7; 6)	1 (1; 0)	4 (4; 0)	10 (6; 4)
Engine development / mechanics / automobile industry	2 (1; 1)	2 (2; 0)	1 (1; 0)	7 (7; 0)
Brass alloys, beryllium-containing alloys (galvanic industry, ship yards, metal processing)	4 (4;0)	1 (1; 0)		14 (8;6)
Metallurgic factory	2 (1;1)			4 (1;3)
Aircraft production and maintenance	3 (2; 1)			2 (2; 0)
Non sparking tools	1 (1; 0)		1 (1; 0)	1 (1; 0)
Radiation shielding	1 (0; 1)	1 (1; 0)		
Military vehicle armor	2 (1; 1)			
Fluorescent lamps	2 (1; 1)			
Microelectronics/ electrical relays	1 (1; 0)	1(1; 0)		8 (6; 2)
Chemical industry (additive to glass, ceramics, plastics/ catalyst)	1 (1; 0)			
Engraving of gems	1 (1; 0)			
Ore mining	1 (1; 0)			1 (1; 0)
Grinding of optical lenses for precision instruments		1 (1; 0)		1 (1; 0)
Indirect (contaminated garments)				2 (2; 0)

Values represent number of individuals and numbers in brackets show number of individuals in

Germany and Israel, respectively.