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CLINICAL VIGNETTE

Beryllium: Genetic Variation to Susceptibility

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Case Report

A 72-year-old African American man presented with long-standing dyspnea and cough that had increased over the preceding year. He had multiple chronic medical problems including diabetes type 2, high blood pressure, hypercholesterolemia and chronic back pain and he was taking multiple medications including metformin, verapamil, insulin glargine, hydralazine and furosemide. Because he had worked for decades in the aircraft & satellite construction industry, he was evaluated for possible beryllium lung disease.

The patient was eventually diagnosed with pulmonary tuberculosis and successfully treated. However, beryllium can cause symptoms similar to tuberculosis and should be considered by clinicians in a patient with the appropriate exposure history. An interesting aspect of beryllium disease is individual variability in susceptibility. This paper will provide an overview of beryllium's properties and the clinical states of beryllium sensitization and chronic beryllium disease. The role of genetic variations in the human leukocyte antigen (HLA), tumor necrosis factor alpha (TNF-α), T cell receptor and transforming growth factor beta one in determining human susceptibility to beryllium will also be explored.

Beryllium properties

A grayish metal, beryllium is the fourth element on the periodic table. Emerald and aquamarine are gem-quality forms of beryllium. The oxide form of beryllium was discovered in 1798 by Vauquelin. Because of its strength, lightness, high melting point (1287°C), electrical conductivity and anti-corrosive properties, beryllium is an attractive component in many high-tech industries such as aircraft, spacecraft, and electronics.[1]

Beryllium occurs naturally. The major environmental source is derived from fossil fuel combustion.[2] Beryllium is water insoluble and adsorbs tightly to soil such that it is usually not a drinking water contaminant.[2] Beryllium is not significantly bioaccumulated in the food chain.[2]

Beryllium toxicity

The harmful effects of beryllium was first observed[3] in the 1930's. Acute lung injury in occupationally exposed beryllium workers led to the adoption of safety standards. The current Occupational Safety & Health Administration workplace standard of 2 mcg/m[3] for an 8-hour shift is based on the experiences of acute lung injury from[2] the 1930's. However, despite the safety guideline, some workers developed a form of chronic beryllium injury.

Sensitization and chronic disease

Humans chronically exposed to beryllium can develop beryllium sensitization and/or chronic beryllium disease. About 1% to 5% of exposed beryllium workers develop beryllium sensitization.[4] After a variable period of 4 to 30 years, most persons sensitized develop chronic beryllium disease, which is characterized by noncaseating granulomas in the lung.[5] However, individuals with presumed negligible beryllium exposure (i.e., secretaries and security staff at beryllium facilities, and family members of beryllium workers) also may develop beryllium sensitization and chronic beryl-

lium disease. The non-linearity between beryllium exposure and the development of beryllium sensitization/ chronic beryllium disease suggests that a dose response may not exist[2], and that some may have a genetic susceptibility to beryllium's harmful effects.[3]

Beryllium sensitization

Beryllium exposure can cause a type IV hypersensitivity reaction, a cell-mediated immune response by beryllium-specific T lymphocytes.[6] The hypersensitivity reaction can be detected using the beryllium lymphocyte proliferation test. Developed in the 1980's, the beryllium lymphocyte proliferation test measures in vitro the degree of proliferation of blood cells (or bronchoalveolar lavage cells).[7] In beryllium lymphocyte proliferation tests, a person's blood lymphocytes are exposed to varying concentrations of beryllium and assessed for the amount of titriated thymidine incorporation.[7] Unexposed and unsensitized persons do not demonstrate a proliferation. While the specificity is high (97%), the beryllium lymphocyte proliferation test's specificity[2] is relatively low (68%). The positive predictive value of the beryllium lymphocyte proliferation test is[5] approximately 12%.

Chronic beryllium disease

A person may have beryllium sensitization without evidence of chronic beryllium disease. Persons with beryllium sensitization have no detectable clinical abnormalities. Beryllium sensitization progresses to chronic beryllium disease at a rate of 6% to 8% per year.[2] Beryllium sensitizationides involving the lung, noncaseating granulomas may develop in the dermatologic, hepatic, cardiac, and hematologic/lymphatic systems.[2] Complications of chronic beryllium disease may eventually lead to the individual’s demise, most commonly due to terminal lung disease.[2]

Conceptual Model for Genetic Susceptibility - The Tri-molecular Complex

In the human body, beryllium is presented by an antigen presenting cell (probably pulmonary dendritic cells) via the human leukocyte antigen (HLA) molecules to the CD4+ T cell receptor.[7] The tri-molecular complex of HLA-beryllium-T cell receptor is believed to be necessary for the activation of beryllium-specific T cells which are pivotal in the development of beryllium sensitization and chronic beryllium disease.[7] Variations in the HLA molecule and the T cell receptor form the basis for understanding genetic susceptibility to beryllium.

Role of HLA

HLA Class II molecules have 3 isotypes designated HLA-DP, -DQ and -DR. The HLA genes are among the most polymorphic of the human genome. Genetic variations in the HLA isotypes were first discovered to increase the risk of certain diseases approximately 30 years ago (HLA-DP3 increased the relative risk of Hodgkin's disease by two-fold).[8] Since the initial discovery, over 500 diseases have been shown to have HLA associations.[8] Many clinicians are familiar with the association of ankylosing spondylitis and HLA-B27.

HLA-DPB1

The possible association of HLA Class II molecule with beryllium sensitization and/or chronic beryllium disease was evaluated by epidemiological methods. Richeldi et al found that the majority of chronic beryllium disease patients (97% vs. 33% in beryllium-exposed controls) had HLA-DPB1 with a glutamic acid residue at position 69 of the β chain[9] (Glu69). Later studies confirmed the association of HLA-DPB1(Glu69) with an increased risk of beryllium sensitization/ chronic beryllium disease.[3] However, the allele is also present in about one third of unaffected studied populations.[3] Consequently, the positive predictive value of HLA-DPB1(Glu69) is fairly low[5] at 12%. There are 42 known HLA-DPB1(Glu69) alleles which can be further stratified into risk categories based on charge. HLA-DPB1(Glu69) alleles with the greatest negative surface charge were associated with an increased risk of chronic beryllium disease.[7] HLA-DPB1(Glu69) alleles also significantly determine the depth of the binding cleft for beryllium, possibly increasing the risk for beryllium sensitization/ chronic beryllium disease.[7] HLA-DPB1(Glu69) homozygotes are also at increased risk (3x) compared to heterozygotes.[3]

HLA-DR & -DQ

The role of HLA-DR and -DQ in beryllium sensitization and chronic beryllium disease is less conclusive. HLA-DR alleles with phenylalanine at position 47 of the β chain and alleles with arginine at position 74 of the β chain have been linked to increased beryllium sensitization but not chronic beryllium disease.[4] A single report found that HLA-DQ with glycine at position 86 of the β chain may be a marker for progression from beryllium sensitization to chronic beryllium disease.[4]

The T Cell Receptor

The T cell receptor binds noncovalently to the HLA-antigen complex via 3 complementary-determining regions. The complementary-determining regions play a major role in determining the specificity of the T cell receptor. The identity of a beryllium-specific T cell receptor was determined by Fontenot et al.[10] Using anti-T cell receptor monoclonal antibodies, Fontenot found a skewing of the T cell receptor repertoire in the bronchoavleolar cells of chronic beryllium disease subjects compared to blood. An expansion of the T cell receptor VB3 was found in 11 of 28 chronic beryllium disease subjects. A conserved amino acid sequence of cysteine at position 90, glycine or lysine at position 95, aspartic acid at position 96, and arginine or glutamine at position 97 was found in 4 subjects, indicating a beryllium-specific TC motif. However, the exact role of the T cell receptor motif in beryllium sensitization and chronic beryllium disease are yet to be determined.[4]

The Role of Cytokines - TNF-α

The conceptual model described earlier highlights some of the potential roles of cytokines in beryllium sensitization and chronic beryllium disease. The beryllium sensitization studied cytokines in beryllium sensitization and chronic beryllium disease are TNF-α and TGF-β1. TNF-α is a potent pro-inflammatory cytokine that is believed to be important in the pathogenesis of beryllium sensitization and chronic beryllium disease. Therefore polymorphisms in the gene that alter the levels of TNF-α production may affect an individual's response to beryllium. This hypothesis was confirmed in a small study. Maier et al identified chronic beryllium disease patients with increased TNF-α levels as associated with worse clinical markers of disease severity.[11] The TNF-α*02 allele in the promoter region was a functional polymorphism that seemed to correlate with chronic beryllium disease severity. However, the small sample size limits the generalizability of the study.[4]

TGF-β1

TGF-β1 is a multifunctional cytokine, modulating cell growth, cell differentiation, fibrosis and immune response. As with TNF-α, polymorphisms in the TGF-β1 gene are believed to be potential determinants of an individual's response to beryllium. Jonth et al identified single nucleotide polymorphisms of the TGF-β1 gene that affect its production.[12] -509 and codon 10T are associated with lower serum TGF-β1 levels but higher disease severity in chronic beryllium disease.[12] Meanwhile -509T and codon 10C appears to provide relative protection, associated with higher levels of TGF-β1 and lower disease severity.[12] These observations suggest TGF-β1 modulate the inflammatory response to beryllium. TGF-β1 polymorphisms have not been associated with increasing an individual's susceptibility to beryllium sensitization/ chronic beryllium disease, but rather appear to modify the disease severity.[7]

Conclusion

Beryllium's desirable technical qualities will likely ensure its continued use in the high-tech industries. Our understanding of beryllium's harmful effects has evolved from an acute model of acute lung injury to a chronic model of beryllium sensitization and chronic beryllium disease. Awareness of prior beryllium exposure can help in the differential diagnosis. The susceptibility of individual patients seems to be strongly tied to the presence of genetic variations, in particular, HLA-DPB1(Glu69). The role of HLA-DR and -DQ as determinants of susceptibility seems to be less significant. Variations in the T cell receptor, TNF-α and TGF-β1 seem to be important factors in beryllium pathogenesis but less well-understood at this time.

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