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Myeloperoxidase Deficiency

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Introduction

Myeloperoxidase (MPO) is a hemoprotein expressed in azurophilic granules of neutrophils and in the lysosomes of monocytes. The enzyme has strong antibacterial properties and is unique in its ability to generate potent bactericidal compounds such as hypochlorous acid (HOCl) from hydrogen peroxide and the halide, chloride.

Myeloperoxidase deficiency, first described in 1954 is an autosomal recessive disorder caused by mutations in the MPO gene on chromosome 17. It is the commonest inherited defect of phagocytes. Patients with MPO deficiency have impaired microbial killing, but the majority are asymptomatic clinically except if they are also diabetic. In this review, we provide an update on this common phagocyte disorder.

Etiology

MPO encoded by a single gene located on band 17q22-23 is a tetramer of 150 kDa consisting of two heavy chains, two light chain subunits, and two iron atoms. The MPO gene encodes for a single translational product that after glycosylation and proteolytic processing is packaged as mature MPO in the azurophilic granules. MPO production is determined by various genetic mutations and deletions. MPO, once released by activated leukocytes, utilizes the oxidative potential of its co-substrate hydrogen peroxide in the peroxidation and halogenation cycles to generate the cytotoxic oxidant species and potent bactericidal compound hypochlorous acid (HOCl) along with other toxic oxidants that are capable of not only initiating lipid peroxidation but also promoting a series of post-translational modifications, such as halogenation, nitration, and oxidative cross-linking to target proteins at sites of inflammation. The toxicity and bactericidal activities of HOCl occur due to its potential to modify lipids, DNA, amines, and tyrosine into halohydrins, 5-chlorouracil, chloramines

and 3-chlorotyrosine respectively.

Primary MPO deficiency is inherited as an autosomal recessive disorder and is generally present with varying degree of severity and clinical features. A number of point germline mutations resulting in MPO deficiency have been detected in primary form. Some of these mutations are associated with the defective posttranslational processing of the MPO precursor protein and others with pre-translational defects caused by mutations in the regulatory portion of the *MPO* gene. Most of the mutations associated with hereditary form are R569W (the commonest), Y173C, M251T, G501S, and R499C and a deletion of 14 bases (D14) within exon 9. It is noteworthy that eosinophils are never involved in MPO deficiency since eosinophil peroxidase is encoded by another gene than MPO.

A secondary MPO deficiency is less common than the hereditary form but may develop due to somatic mutations of the MPO gene. In most cases, the deficiency is partial and affects only a proportion of neutrophils. The acquired form is usually transient and generally resolves once the underlying condition improves.

The various disorders that can lead to acquired or secondary MPO deficiency include diabetes mellitus, pregnancy, iron deficiency, renal transplantation, thrombotic diseases, lead poisoning, obstructive jaundice, disseminated cancers, hematologic disorders and neoplasms such as acute and chronic myeloid leukemia, myelodysplastic syndrome, polycythemia vera, Hodgkin lymphoma, severe infections, cytotoxic agents, and some anti-inflammatory drugs like sulfapyridine.

Epidemiology

MPO deficiency was adjudged as an extremely rare disease, and only 17 known cases had been reported up to 1979. In the United States and Europe, an estimated frequency is 1 per 2,00 to 4,000 individuals, and in the Japanese population, it is 1 per 55,000 people. However, modern diagnostic techniques have provided a better approach to the diagnosis of this disorder, and it is a more common condition than initially believed.

Pathophysiology

Neutrophils are considered as the first line of defense against pathogens, and during phagocytosis, they undergo a process termed the respiratory burst in which most bacteria are killed and digested in the phagosomes. The MPO-enriched azurophilic granules in neutrophils fuse with the phagosome and are released into the phagosomes when the common

membrane is ruptured. These neutrophils, after encountering pathogens, generate a respiratory burst via activation of NADPH oxidase that leads to the production of superoxide, hydrogen peroxide, and other reactive oxygen derivatives such as HOCI, a primary product of MPO activity. The antimicrobial activities of MPO-HOCl not only restricted to killing bacteria but also fungi, viruses, erythrocytes, tumor cells, natural killer (NK) cells and platelets indicates its role in the innate immune response. Reports have also shown that MPO is involved in terminating the respiratory burst since individuals with MPO-deficient neutrophils have a prolonged respiratory burst, and an increase in hydrogen peroxide production.

MPO-derived HOCl has been shown to be the required source of ROS for neutrophil extracellular traps (NETs), that are DNA structures released due to de-condensation of chromatin formation, that not only trap bacteria, but also regulates both the innate and adaptive immune response in many ways.

MPO is believed to play a role in suppressing of the adaptive immune response as demonstrated by two models of enhanced T cell-mediated skin delayed-type hypersensitivity and antigen-induced arthritis in Mpo−/− mice. Mechanistically, MPO released from neutrophils inhibits LPS-induced DC activation as measured by decreased IL-12 production and CD86 expression consequently, limiting T cell proliferation and proinflammatory cytokine production. In contrast, a pathogenic role for MPO in driving autoimmune inflammation was demonstrated using MPO-deficient mice in the K/BxN arthritis and collagen-induced arthritis (CIA) models exhibiting reduced disease severity. Also, increased MPO levels and activity have been observed in many inflammatory conditions and autoimmune diseases including multiple sclerosis (MS) and rheumatoid arthritis (RA).

MPO plays a role in modulation of vasculature functioning, associated with chronic vascular diseases such as atherosclerosis. In the extracellular matrix (ECM), MPO works as a nitric oxide(NO)-scavenger consuming NO that leads to impaired endothelial relaxation. MPO and its oxidative species present in the atherothrombotic tissue, promotes lipid peroxidation, conversion of LDL to a highly-uptake atherogenic form, selectively modulates Apolipoprotein A-I (apoA-I) generating dysfunctional HDL particles more susceptible to degradation and impairs the ability of apoA-I to promote cholesterol efflux. Moreover, elevated systemic levels of MPO and its oxidation products are associated with increased cardiovascular risk. However, the measurement of MPO as a cardiovascular risk marker has not generally been accepted like the more standardized assay for high sensitive C-reactive protein.

History and Physical

The majority of patients with MPO deficiency are asymptomatic with no increase in infections. However recurrent severe infections with Candida Albicans have been observed only in patients who also suffered from other conditions such as diabetes mellitus. Thus, in these patients, it is not clear if the infections were a mere outcome of MPO deficiency or if other MPO independent mechanisms were also responsible. In a study conducted by European researchers, only 50% of the complete MPO deficient patients had infectious complications, the rest were asymptomatic, and only 10% of the patients suffered from life-threatening infectious complications. The lack of serious infections in MPO deficiency compared to CGD emphasizes the importance of the reactive oxygen species such as amplified hydrogen peroxide generation serving as a potent bactericidal agent that protects patients with MPO deficiency. However, the absence of MPO-mediated species such as HOCl appears to be crucial in the failure to abort fungal infections such as Candidiasis.

Evaluation

The first step in diagnosing the MPO deficiency is determination of peroxidase activity by histochemical staining of leukocytes, immunocytochemistry, or, more commonly, flow cytometry which allows assessment of functional MPO within neutrophils. Immunoblotting of isolated leukocytes for MPO protein also provides additional information into the molecular basis of the observed absence of functional enzyme independent of its enzymatic activity.

Differential diagnosis of MPO deficiency from disorders presenting with similar clinical signs and symptoms includes Chediak-Higashi syndrome, Hyperimmunoglobulinemia E, leukocyte adhesion deficiency, neutropenia, neutrophil actin dysfunction, lazy leukocyte syndrome and any condition that can cause secondary MPO deficiency. In any patient with disseminated fungal infections, MPO deficiency should be considered as a differential.

Treatment / Management

Generally, since most individuals with MPO deficiency do not suffer from infections and are typically asymptomatic, prophylactic antibiotics are discouraged and not indicated. However, caution should be taken in patients afflicted with concomitant diabetes mellitus, with a high incidence of localized and systemic infections, where prompt and aggressive treatment with antimicrobials is usually necessary to control infections. It is prudent and cautious to avoid treatments that can increase the propensity of fungal infections such as prolonged use of antibiotics or steroids.

Questions

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