REVIEW ARTICLE

Mendelian Susceptibility to Mycobacterial Diseases

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ABSTRACT

Mendelian susceptibility to mycobacterial diseases is a rare condition often diagnosed in countries where the Bacillus Calmette-Guérin vaccine is given routinely at birth. Although prevalence is difficult to determine, it is estimated that the global prevalence of Mendelian susceptibility to mycobacterial diseases is 1 per 50,000 to 1,000,0000 individuals. In the high-income countries where the Bacillus Calmette-Guérin vaccine is not routinely used, this condition may be diagnosed based on recurrent non-tuberculous mycobacterial infections or recurrent Salmonella infections, often in unusual anatomic sites.

INTRODUCTION

Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is a group of genetic disorders that are an inborn error of immunity. Individuals with MSMD are otherwise healthy with no obvious immunological abnormalities. However, they are at increased risk for infections with environmental mycobacteria. These individuals can go undiagnosed for years unless there is a high index of suspicion due to recurrent infections with certain organisms or the identification of an infection in an uncommon site for that organism.

In countries where the Bacillus Calmette-Guérin vaccine is not routinely recommended, such as the United States, MSMD may go undiagnosed unless there is a high index of suspicion based on the occurrence of certain types and patterns of infections.

CONDITION

The underlying reason for MSMD is 35 separate genetic disorders resulting from mutations in 19 genes. Biallelic mutations are the most common. This condition affects an estimated 1 in 10,000 individuals. Fifty percent of the patients had IL-12Rβ1 or IL-12p40 deficiency. There may be an impaired response to interferon gamma (IFN-ϒ) or the production of IFN-ϒ may be impaired, and the severity of the disease depends on penetration.

Most of these individuals are identified in the first year of life, usually within the first six months of life if they received the Bacillus Calmette-Guérin (BCG) vaccine at birth.

These individuals have normal immunoglobulins and normal dihydrorhodamine and nitroblue tetrazolium tests. They may have lymphopenia, but usually have no other laboratory abnormalities on routine testing. Measuring IFN-ϒ in plasma or serum can help in identifying complete defects when no IFN-ϒ is detected. However, partial defects will not be diagnosed since some IFN-ϒ may be present with partial defects. IFN-ϒ levels should only be performed after an active infection resolves.

The BCG vaccine is routinely recommended at birth in many countries globally where there is a high incidence of tuberculosis. BCG is administered on the left upper arm of the newborn. Currently, BCG is not recommended in the United States. Infants with MSMD can present with two types of diseases. The first is “BCG-itis” (also referred to as loco-regional or isolated infection), which

is a localized lymphadenitis that usually affects the axillary, cervical, or supraclavicular lymph nodes. The second is "BCG-osis" (also referred to as systemic BCG infection), which can cause infection of the lungs, skin, soft tissue, spleen, kidneys, gastrointestinal tract, bone, joints, or brain. In addition, it can result in lymphadenitis of the distant lymph nodes (mesenteric, mediastinal, and inguinal). *Mycobacterium bovis* is often isolated from the site of infection.

Individuals with MSMD are also susceptible to non-typhoidal Salmonella infections that cause gastroenteritis or sepsis. Patients may have recurrent Salmonella infections, especially at unusual sites, such as lymph nodes. In individuals with recurrent non-typhoidal Salmonella infections who have not received BCG, MSMD should be suspected, and the patient referred to a geneticist for evaluation. Infections with unusual or uncommon gram-negative enteric organisms, especially in otherwise healthy individuals, and severe *Mycobacterium tuberculosis* infections, have also been observed in individuals with MSMD. Fungal infections, including Paracoccidioidomyces, Candida, and Histoplasma, have been reported. Therefore, patients with the clinical presentation of chronic mucocutaneous candidiasis should be evaluated for MSMD. There does not appear to be a selective predisposition to severe viral infections.

Henoch-Schönlein purpura has also been reported in individuals with MSMD.

MANAGEMENT

There is no curative treatment for MSMD, although patients benefit from monthly subcutaneous or intravenous immunoglobulin therapy. The benefits of dialyzable leukocyte extracts have also been reported in MSMD patients. Some patients also undergo hematopoietic stem cell transplantation. As one might expect, recombinant human IFN-Y appears to be beneficial in many MSMD cases. There are no clinical trials that have shown a definitive benefit with any of these management modalities.

Management of infections with appropriate antimicrobials is critical since many patients with MSMD succumb to infections as a result of multiorgan failure. Lifelong azithromycin prophylaxis may be successful in preventing recurrences and should be done in consultation with an infectious diseases specialist. Gene therapy could be curative, but it is currently unavailable for MSMD.

Mortality risk in patients with MSMD is variable depending on the specific genetic defect and the clinical outcome of serious infections. In low-income parts of the world where children receive the BCG vaccine at birth, most patients with MSMD die from multiorgan failure secondary to serious infections before their fifth birthday.

To prevent life-threatening complications of BCG infection, BCG vaccination should not be administered to newborns and infants whose siblings or other relatives have had complications of the BCG vaccine, and MSMD was confirmed or suspected.

CONCLUSION

In the United States and other parts of the world where BCG is not routinely recommended, a high index of suspicion is necessary to make the diagnosis of MSMD. MSMD should be suspected in otherwise healthy individuals with recurrent mycobacterial and Salmonella infections or infections in unusual sites with these organisms. In addition, unexplained infections caused by endemic intracellular pathogens like Histoplasma and deep mycoses should raise concern for MSMD.

Author Disclosure: Dr. Rathore has disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

RECOMMENDED READING

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