Mendelian Susceptibility to Mycobacterial Disease: A Clinical and Laboratory Approach

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Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of rare genetic disorders characterized by increased susceptibility to infections with low-virulent mycobacteria like the Bacillus Calmette–Guérin (BCG) vaccines and the nontubercular environmental mycobacteria. These patients are also at increased risk of infections with non-typhoidal Salmonella, Candida, and Mycobacterium tuberculosis. In this article, we provide a clinical and laboratory approach to the diagnosis of MSMD. Various genetic defects causing MSMD and their treatment have been discussed.

Keywords: Disseminated BCG infection, Interferon, Mycobacterial disease.

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Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of genetic disorders characterized by a defect in interferon γ (IFNγ)–mediated immunity, leading to a predisposition to atypical and low virulent mycobacteria. The term MSMD is a misnomer, as these patients are not only susceptible to mycobacterial infections but are at increased risk for infections with other intramacrophagic bacteria including Salmonella, Listeria, Klebsiella, and others. These diseases are characterized by a defect in interferon-γ (IFNγ) production or response to IFNγ.1

IFNγ/IL-12 Pathway

It is essential to understand the functioning of the IFNγ/IL-12 pathway in healthy individuals before we discuss MSMD and its defects.

When macrophages engulf microorganisms, they produce IL-12. IL-12 is a heterodimer of IL-12B (p40 subunit) and IL-12A (p35 subunit). p40 subunit is common for IL-12 and IL-23. IL-12 acts on T and NK cells through its receptor IL-12R. IL-12R is a heterodimer composed of IL-12Rγ1 and IL-12Rγ2. Intracellular signaling through IL-12R is mediated by STAT-4 phosphorylation and results in IFNγ production. IFNγ stimulates macrophages and mediates intracellular killing of microorganisms. IFNγ acts via IFNγ receptor composed of IFNγR1 and IFNγR2. When IFNγ acts on IFNγR1, it facilitates IFNγR1 dimerization. Following this,2 IFNγR2 molecules join this complex. Intracellular signaling is mediated by STAT1 phosphorylation, which translocates to the nucleus and activated IFNγ genes. This results in the activation of macrophages and the killing of microbes within them. This has been schematically represented in Figure 1.

An inability to handle intracellular pathogens due to defects in IFNγ production (IL-12B, IL-12Rγ1, IL-12Rγ2) or response (IFNγR1, IFNγR2, STAT1) result in MSMD.

Types of MSMD

MSMD has been classified based on Table 1 as:
- Pattern of inheritance–AR, AD, XR
- Functional impairment (based on residual response to stimulation of receptor)–complete deficiency, partial deficiency
- Surface expression of protein–absent, reduced, increased.

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cellular response to IFNγ. Some of these mutations are gain of glycosylation defects. Clinically, complete IFNγR1 deficiency resembles the complete IFNγR1 deficiency and has a severe clinical phenotype. Patients are at risk of infections with BCG and EM (M. avium, M. fortuitum) and carry a poor prognosis. HSCT is the treatment of choice. Partial IFNγR2 deficiency is a milder form of the disease and only a handful of cases have been reported to date. These patients do well on interferon γ injections.

**IL-12Rγ1 and IL-12B Deficiency**

Both IL-12 and IL-23 contain p40 subunit (encoded by IL-12B gene) and IL-12Rγ1 chain is present in IL-12R and IL-23R. Thus, mutations in the IL-12B gene or IL-12Rγ1 chain impair the functions of both these cytokines. Patients with IL-12B and IL12Rγ deficiency are at increased risk of BCG disease and salmonellosis caused by nontyphoidal Salmonella. Salmonellosis is noted in more than 50% of these patients, and the higher incidence of Salmonella infection in patients with an impaired IL-12/IL-23 pathway than in patients with an impaired IFNγ pathway suggests that IL-12 and IL-23 may play a particular role in controlling Salmonella infection via IFNγ independent mechanisms (Fig. 1).

AR complete IL-12Rγ1 deficiency is the most common cause of MSMD. The clinical phenotype of this disease is very heterogeneous, ranging from early death in infancy to an asymptomatic course throughout adulthood. Mycobacterial infections are the most frequent infections observed in these patients (BCG), M. avium, M. avium intracellulare complex, M. chelonae, M. fortuitum, M. fortuitum-chelonae complex, M. genevense, M. gordonae, M. tilburgii, M. triplex, M. simiae). The prognosis of this immunodeficiency is variable, but good in most cases. Patients should be treated with prolonged and aggressive antibiotics against mycobacteria in addition to subcutaneous IFNγ. HSCT is not indicated in most of the cases.7

AR complete IL-12B deficiency has a clinical presentation similar to IL-12Rγ1 deficiency. These children present with BCG disease and recurrent salmonellosis. The clinical course is variable, though most patients do well on antibiotics and IFNγ therapy.1

**X-linked Recessive NEMO Deficiency**

NEMO deficiency is typically associated with incontinentia pigmenta (X-linked dominant inheritance) and anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) due to null and hypomorphic mutations, respectively. The E315A and R319Q mutations of NEMO, cause MSMD, wherein patients are at increased risk for atypical mycobacterial infections, especially M. avium.8 Prognosis is variable, and most reported patients have done well on IFNγ injections.

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* Dysfunctional protein, Increased expression

**Table 1:** Brief outline of the common defects causing MSMD

**Fig. 1:** Critical pathways in controlling mycobacterial infection
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Rarer causes of MSMD
AR ISG15 deficiency, AD IRF8 deficiency, AD STAT1 deficiency, AR SPPL2A deficiency, AR TYK2 deficiency, and XR CYBB deficiency are rare causes of MSMD. The available literature is based on a few case studies.1,8

Syndromic MSMD
It is typically defined as a combination of both mycobacterial disease and other infections associated with a more complex cellular phenotype. AR STAT1 and TYK2 deficiencies, AD GATA2 deficiency, and recently described RORγ/RORγT and JAK1 deficiencies present with syndromic MSMD. These patients are characterized by atypical mycobacterial infections, viral infections, chronic mucocutaneous candidiasis, and other abnormalities.9

When should one think of MSMD?
- Disseminated BCG infection
- Infections with environmental mycobacteria
- Recurrent salmonellosis (caused by non-typhoidal salmonella)
- Osteomyelitis caused by atypical mycobacteria
- Infections with intracellular pathogens—mycobacteria, virus, fungi (candida)
- With normal immunological screen (immunoglobulins, lymphocyte subsets, and tests for the chronic granulomatous disease being normal).

Laboratory Approach

Flow Cytometry for Protein Expression
IL-12Rγ1 and IFNγR1 protein expression can be studied by flow cytometry. Absent IL-12Rγ1 expression on T cells is diagnostic of IL-12Rγ1 deficiency with a sensitivity of 95%. AR complete IFNγR1 deficiency is characterized by absent protein expression while increased expression is noted in AD variety, due to defective recycling of receptors.

Flow Cytometry for Evaluation of Pathways
Study of pathways involved in IL-12 and IFNγ signaling can provide a clue to the underlying defect. Using flow cytometry, one can study phosphorylated STAT1 after IFNγ stimulation and phosphorylatedSTAT4 by IL-12 stimulation. Decreased STAT1 phosphorylation would suggest there is a possible defect in either STAT1, IFNγR1 or IFNγR2. Decreased STAT4 phosphorylation can occur in cases of IL-12 receptor deficiency.

Functional studies may be carried out in research laboratories by evaluating the response to INFγ and patients can be classified into complete and partial deficiencies. This would have an implication in their clinical management.

Genetic studies can be done by next-generation sequencing technology and confirmed by Sanger sequencing.

Conclusion
Children and adults with disseminated BCG infection and infections with atypical mycobacteria must be evaluated for MSMD. These patients are also predisposed to salmonellosis and other intracellular pathogens. AR complete IFNγ deficiency (IFNγ R1 and R2) present with severe infections in early childhood and warrant HSCT. Partial IFNγ R1 and R2 deficiencies have milder phenotype and can be managed with IFNγ injections. IL12Rγ1 deficiency is the most common cause of MSMD and has a variable clinical course. With the advancement of molecular genetics, newer causes of MSMD are being increasingly recognized.

References