High Levels of Interferon Gamma in the Plasma of Children With Complete Interferon Gamma Receptor Deficiency

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ABSTRACT. We have found that children with complete interferon gamma (IFNγ) receptor deficiency, unlike patients with other genetic defects predisposing them to mycobacterial diseases, have very high levels of IFNγ in their plasma. This unexpected observation provides a simple and accurate diagnostic method for complete IFNγ receptor deficiency in children with clinical disease caused by bacille Calmette-Guérin vaccines or environmental nontuberculous mycobacteria. Pediatrics 2001;107(4). URL: http://www.pediatrics.org/cgi/content/full/107/4/e48; interferon gamma, mycobacteria, genetic susceptibility, immunodeficiency, plasma.

ABBRVIATIONS. BCG, bacille Calmette-Guérin; NTM, nontuberculous mycobacteria; IFN, interferon; IL, interleukin; ELISA, enzyme-linked immunosorbent assay.

Mendelian susceptibility to mycobacterial infection (MIM 209950) is a rare and heterogeneous syndrome.1−3 Affected individuals develop severe clinical disease caused by weakly virulent mycobacterial species, such as bacille Calmette-Guérin (BCG) vaccines and environmental nontuberculous mycobacteria (NTM). The clinical phenotype ranges from fatal disseminated infection in early childhood to focal recurrent infection in adults. In the last 5 years, considerable genetic heterogeneity has been documented. Mutations have been found in 4 genes: IFNGRI, encoding the interferon gamma (IFNγ) receptor ligand-binding chain; IFNGR2, encoding the IFNγ receptor signal-transducing chain; IL12B, encoding the p40 subunit of interleukin (IL)-12; and IL12RB1 encoding the IL-12 receptor β1 chain. Different types of mutations define 8 inherited disorders: complete recessive IFNγR1 deficiency with4−6 or without7 receptor surface expression; partial, as opposed to complete, IFNγR1 deficiency with recessive6 or dominant inheritance7; complete recessive IL-12p40 deficiency; and IL-12Rβ1 deficiency.13,14 However, a molecular etiology is still lacking for a majority of the patients. Complete IFNγR17−7 and IFNγR28 deficiency are responsible for early-onset overwhelming mycobacterial disease. Partial IFNγR1 defects8,9 and partial IFNγR2 deficiency,11 like complete IL-12p40 deficiency and IL-12Rβ1 deficiency,13,14 are responsible for milder clinical forms.1−3

The diversity of the genes and pathogenic mutations involved renders molecular diagnosis challenging. For example, complete IFNγR1 deficiency may be caused by mutations preventing expression of the receptor4−6 or binding of the surface receptor to IFNγ.7 Moreover, cells with complete IFNγR deficiency do not respond to IFNγ4−7 whereas cells with partial IFNγR deficiency respond to IFNγ at high concentration.8,9,11 Finally, most patients display low levels of IFNγ production by peripheral blood cells.1,2 Cumbersome diagnostic investigations combining highly specialized functional, biochemical, and genetic assays are, therefore, required in most patients with the syndrome. An accurate and rapid molecular diagnosis is, however, essential for the rational and efficient treatment of the patient. Indeed, children with complete IFNγR deficiency do not achieve sustained remission with antibiotics alone and do not respond to exogenous IFNγ, resulting from a lack of functional receptors. The outcome seems to be often fatal and bone marrow transplantation should be considered.1−3,15 In contrast, the administration of subcutaneous IFNγ together with antibiotics is often beneficial in patients with other genetic defects, and full remission of mycobacterial disease has been achieved.1−3 The lack of a simple method for rapidly discriminating between patients with complete IFNγR deficiency and patients with other genetic etiologies greatly compromises the management of these patients.

We measured IFNγ by enzyme-linked immunosorbent assay (ELISA) in the plasma of healthy individuals and patients with various forms of Mendelian susceptibility to mycobacterial infection. IFNγ is undetectable (<5 pg/mL) in the serum and plasma of 6 healthy individuals tested (not shown). All patients had suffered from BCG and/or NTM clinical disease when the blood sample was taken. Patients with IL-12p40 (n = 3) and with IL-12-receptor β1 chain deficiency (n = 5)—like patients with partial dominant IFNγR1 deficiency (n = 7) and partial re-
IFN-γ R2 deficiency (n = 1)—had no detectable IFN-γ in the plasma (Fig 1). We found low levels of IFN-γ (median = 57 ± 9.9 pg/mL) in the plasma of patients with partial recessive IFN-γ R1 deficiency (n = 2). Remarkably, we found very high levels of IFN-γ in the plasma of patients with complete IFN-γ R1 deficiency (n = 5; median = 252 ± 113 pg/mL) and complete IFN-γ R2 deficiency (n = 2; median = 433 ± 306 pg/mL). To validate these results, we measured IFN-γ in the serum of 40 other children with unexplained BCG and/or NTM clinical disease. High levels of IFN-γ were found in 1 child, who was subsequently diagnosed with complete IFN-γ R1 deficiency (n = 6; median 249 ± 101 pg/mL). Complete IFN-γ R deficiency was functionally and genetically excluded in the remaining 39 patients.

These results may reflect the more severe course of mycobacterial disease in patients with complete IFN-γ R deficiency, resulting in more intense and sustained IFN-γ secretion. However, high plasma levels of IFN-γ (35 pg/mL) in 1 asymptomatic child with a family history, diagnosed at birth suggests that it is not the case (not shown). Paradoxically, patients with complete IFN-γ R deficiency have previously been shown to have impaired secretion of IFN-γ attributable to a secondary defect in IL-12 production.6 As IFN-γ R is ubiquitously expressed in the organism, our results suggest that patients with complete IFN-γ R deficiency cannot eliminate blood IFN-γ, resulting from a lack of binding (IFN-γ R1 deficiency) or a lack of internalization (IFN-γ R2 deficiency) of the cytokine. This would also account for the detectable levels of IFN-γ in the plasma of patients with partial recessive IFN-γ R1 deficiency, in whom the receptor mutation probably reduces but does not abolish the affinity of the receptor for IFN-γ.6 Receptors from patients with dominant IFN-γ R1 deficiency probably bind and/or recycle sufficient amounts of IFN-γ to keep serum levels undetectable. Profound defects of IFN-γ production (IL-12p40 and IL-12Rβ1 deficiencies) in patients with functional IFN-γ receptors are not associated with high levels of IFN-γ in the plasma.

In any event, plasma IFN-γ determination by ELISA is a simple, cheap, rapid, and efficient way to guide molecular diagnosis and to provide a rational basis for the treatment of patients with Mendelian susceptibility to mycobacterial infection. High levels (our threshold of 80 pg/mL is >2 standard deviations above the mean level in patients with partial recessive IFN-γ R1 defects) of IFN-γ in the serum of a patient with BCG and/or NTM clinical disease should lead to the consideration of bone marrow transplantation options while searching for and validating null mutations of IFNGR1 or IFNGR2. Undetectable or low levels of IFN-γ should lead to the child being treated with subcutaneous IFN-γ while searching for mild mutations of IFNGR1 and IFNGR2, or null mutations of IL12B and IL12RB1.

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