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.

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 recessive8 or dominant inheritance9; recessive complete10 or partial11 IFNγR2 deficiency; complete recessive IL-12p4012; and IL-12Rβ1 deficiency.13,14 However, a molecular etiology is still lacking for a majority of the patients. Complete IFNγR11–7 and IFNγR28 deficiency are responsible for early-onset overwhelming mycobacterial disease. Partial IFNγR1 defects9,9 and partial IFNγR2 deficiency,11 like complete IL-12p4012 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 IFNγ7. 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-
cessive IFNγR2 deficiency ($n = 1$)—had no detectable IFNγ in the plasma (Fig 1). We found low levels of IFNγ (median $= 57 \pm 9.9$ pg/mL) in the plasma of patients with partial recessive IFNγR1 deficiency ($n = 2$). Remarkably, we found very high levels of IFNγ in the plasma of patients with complete IFNγR1 deficiency ($n = 5$; median $= 252 \pm 113$ pg/mL) and complete IFNγR2 deficiency ($n = 2$; median $= 433 \pm 306$ pg/mL). To validate these results, we measured IFNγ in the plasma of 40 other children with unexplained BCG and/or NTM clinical disease. High levels of IFNγ were found in 1 child, who was subsequently diagnosed with complete IFNγR1 deficiency ($n = 6$; median $= 249 \pm 101$ pg/mL). Complete IFNγR 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 IFNγR deficiency, resulting in more intense and sustained IFNγ secretion. However, high plasma levels of IFNγ (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 IFNγR deficiency have previously been shown to have impaired secretion of IFNγ, attributable to a secondary defect in IL-12 production.6 As IFNγR is ubiquitously expressed in the organism, our results suggest that patients with complete IFNγR deficiency cannot eliminate blood IFNγ, resulting from a lack of binding (IFNγR1 deficiency) or a lack of internalization (IFNγR2 deficiency) of the cytokine. This would also account for the detectable levels of IFNγ in the plasma of patients with partial recessive IFNγR1 deficiency, in whom the receptor mutation probably reduces but does not abolish the affinity of the receptor for IFNγ.8 Receptors from patients with dominant IFNγR1 deficiency probably bind and/or recycle sufficient amounts of IFNγ to keep serum levels undetectable. Profound defects of IFNγ production (IL-12p40 and IL-12Rβ1 deficiencies) in patients with functional IFNγ receptors are not associated with high levels of IFNγ in the plasma.

In any event, plasma IFNγ 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 IFNγR1 defects) of IFNγ 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 IFNγ should lead to the child being treated with subcutaneous IFNγ while searching for mild mutations of IFNGR1 and IFNGR2, or null mutations of IL12B and IL12RB1.

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