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Susceptibility to mycobacterial infection in a young man with a hypoglossal nerve palsy: the hunt for an immunological defect

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This case report highlights the immunological considerations in patients who are diagnosed with disseminated infection due to BCG or environmental mycobacteria.

Case history

A 17-year-old boy presented with a four-week history of neck pain, difficulty chewing and deviation of his tongue to the right. On examination there was tenderness of the mid-cervical spine and a right XII nerve palsy. A 6 cm lesion was noted over the left deltoid (Figure 1). There was no lymphadenopathy or splenomegaly. Blood tests were normal apart from ESR 44 mm/h and CRP 83mg/L.

Cervical spine X-rays showed increased space between the odontoid peg and the arch of C1. CT of the cervical spine at 9 months indicated fusion of the right occiput to C1. Triple therapy was continued for 1 year followed by rifampicin + isoniazid for a further year. Nuclear magnetic spectroscopy 1 year after discontinuing therapy showed improvement and the patient remains well.

He had no history of infection with bacteria, viruses or fungi, suggesting an isolated predisposition to mycobacteria. He was HIV-negative with normal immunoglobulin levels, IgG subclasses, complement levels and normal levels of specific antibodies to all the childhood vaccinations. Lymphocyte subsets showed generalized depression, attributed to disseminated infection, but normal percentages. Major histocompatibility complex class I & II expression was normal. He had normal adenosine deaminase and purine nucleoside phosphorylase levels, normal lymphocyte proliferative responses, normal neutrophil oxidative burst function and normal Toll-like receptor (TLR) 4 and TLR 7/9 screening by CD62L shedding assay.
The patient’s brother had also experienced an extensive cutaneous reaction to BCG and both were screened for defects in the IL-12/IFN-γ pathway, described below. Known defects were excluded. Anti-IFN-γ autoantibodies were weakly positive but unlikely to be significant.

**Discussion**

Disseminated infection caused by BCG or environmental mycobacteria (EM) suggests a primary or acquired immunodeficiency, such as severe combined immunodeficiency, chronic granulomatous disease or HIV. A leaky cellular immunodeficiency was considered in the above case but immunological investigations were normal as listed. Given the isolated predisposition to BCG in two siblings, with no other demonstrable immune defect, an inherited deficiency in the IL-12/IFN-γ axis was considered most likely. Such disorders have been described relatively recently and are termed ‘Mendelian susceptibility to mycobacterial disease’ (MSMD). In addition to BCG and EM, affected individuals are prone to extra-intestinal disease caused by non-typhoidal *Salmonella*.\(^1\) In this patient’s case, screening excluded currently known deficiencies of the IL-12/IFN-γ axis, suggesting a novel defect.

**The IL-12/IFN-γ pathway**

Dendritic cells and macrophages act as antigen-presenting cells (APCs) which recognize invading mycobacteria through pattern recognition receptors. Signal transduction leads to activation of the APC and production of IL-12 and IL-23.\(^2\) These cytokines bind to their receptors on T-helper and natural killer cells, inducing production of IFN-γ. The IL-12 receptor (IL-12R) is a complex of IL-12Rβ1 and IL-12Rβ2.\(^3\) IL-12 consists of p40 and p35 subunits which bind to IL-12Rβ1 and IL-12Rβ2, respectively.

Secrete IFN-γ binds to its receptor (IFN-γR) on dendritic cells and macrophages, activating microbicidal mechanisms. The IFN-γR is composed of two chains, IFN-γR1 and IFN-γR2.\(^2\)

**Mendelian susceptibility to mycobacterial disease**

Mutations have been identified in six genes: IFNGR1 and IFNGR2 (encoding IFN-γR1 and IFN-γR2), STAT1 (encoding signal transducer and activator of transcription-1: Stat-1), IL12P40 (encoding IL-12p40), IL12RB1 (encoding IL-12Rβ1) and NEMO (encoding nuclear factor-κB-essential modulator: NEMO).\(^1,3\) Mutations may be associated with partial or complete deficiency of the gene product.

**IFN-γR1 and IFN-γR2 deficiency**

Complete recessive deficiency of IFN-γR1 or IFN-γR2 presents with early severe, often fatal, infection with BCG and EM.\(^1\) There is no cellular response to IFN-γ in vitro.\(^1\) Haematopoietic stem cell transplantation has been curative in a few cases.\(^4\)

Partial recessive IFN-γR1 deficiency diminishes the cellular response to IFN-γ.\(^5\) Patients present with less severe mycobacterial infection which usually responds to antimicrobials +/− IFN-γ.\(^3\)

Dominant IFNGR1 mutations produce truncated receptors with a weak cellular response to IFN-γ.\(^1,3\) Children develop moderately severe infection with BCG and EM.\(^6\) *M. avium* osteomyelitis has been repeatedly described.\(^6\) Outcome is generally good with antimicrobials +/− IFN-γ.\(^3\)

Partial recessive IFN-γR2 deficiency has been reported in a child who presented with mild BCG and *M. abscessus* infection.\(^7\) Partial dominant IFN-γR2 deficiency has been described in one family, causing *M. abscessus* osteomyelitis in one of two homozygous siblings, and disseminated CMV and *M. avium* infection in the other.\(^8\)
Stat-1 deficiency
Stat-1 is a downstream signalling molecule for IFN-γ. Dominant STAT1 mutations cause a partial deficiency with a mild clinical phenotype.1,9

IL-12p40 and IL-12Rβ1 deficiency
Recessive mutations in IL12B result in complete deficiency with undetectable IL-12p40.1 Recessive mutations in IL12RB1 result in complete IL-12Rβ1 deficiency, with no cellular response to IL-12.3 In both cases infection with BCG or Salmonella is common and usually responds to antimicrobials and IFN-γ.1,3

X-linked recessive MSMD: mutations in NEMO
NEMO is a regulatory subunit of the nuclear factor-κB (NFκB) inhibitor kinase complex which controls activation of the transcription factor NFκB, implicated in various immunological pathways.2 Mutations in NEMO have been associated with predisposition to mycobacterial infection.10

Conclusion
We speculate that the case presented represents a novel variant of MSMD. Patients with disseminated or recurrent infection due to BCG or EM, with a severe persistent cutaneous reaction to BCG, or with extra-intestinal infection caused by non-typhoidal Salmonella, should be investigated for a defect in cell-mediated immunity. Consider screening for MSMD, after exclusion of HIV, particularly if family members are symptomatic.

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