

## First Report of Impaired Interferon Gamma-Mediated Immunity in Mexico.

Aldana R., López-Enriquez C\*, Karam J. and Arbo A.

Department of Infectious Diseases and Neumology Service. Hospital Infantil de México Federico Gómez. Mexico City, Mexico.

We report the case of a 33-month-old-girl who was admitted in our hospital with history of fever and lymphadenomegaly that began at 6 months of age. She was born in 2001 and was the first child of a healthy, unrelated, middle-class, white mexican parents without consanguinity living in a urban area of Mexico.

Weight, height and psychomotor development were normal until 1 year old, as well as the immunizations (for tuberculosis with bacille Calmette-Guérin (BCG), attenuated poliovirus, diphtheria-pertussis-tetanus-haemophilus influenzae-hepatitis B and measles-mumps-rubella) were up to-date. There was no history of transfusions, allergies, exanthematic diseases, recent travel, animal contact, or known exposure to *Mycobacterium tuberculosis*.

At the age of 6 months, she presented right axilar lymphadenomegaly and fever. Two months later axilar nodule was removed and biopsy revealed lymphoepithelioid granulomas. With the diagnosis of ganglionic tuberculosis, treatment with rifampin, isoniazid and pyrazinamid was initiated. Ten months later, at the age of 18 months, she developed fatigue and enlargement in both axilar and cervical areas and clarithromycin was added to the previous antimicrobial regimen. At the age of 24 months, treatment was ended with only partial response. At 31 months of age, due the persistant enlargement of cervical adenopathy, a new biopsy was done. Direct observation of the tissue (Ziehl-Neelsen stain) showed numerous acid-fast bacilli. Preliminary report of the microbiology lab informed *Mycobacterium tuberculosis hominis* resistant to isoniazid, and a new treatment with rifampin, streptomycin, ethambutol and ciprofloxacin was began.

Two months later, she was admitted for first time to our hospital for a 10-days history of daily fever, decreased appetite, malaise and night sweats. Physical examination revealed fever, moderate respiratory distress, oral candidiasis, cervical and axilar lymphadenomegaly, hepatomegaly and splenomegaly. Purulent discharge was noted on the surgical incision of the previous cervical biopsy. Rest of physical examination was normal.

Lab results reported anemia (Hb 9 gr/dl), leukocytosis (WBC 15,000/mm<sup>3</sup>), neutrophilia (70%) with left side desviation, and hypoalbuminemia. Serum electrolyte levels as well as renal and liver function test were normal.

A CAT scan was performed showing enlarged ganglionic nodules in both lungs and abdomen. Results of a tuberculin skin test (TST) and HIV test (ELISA) were negative. Several immunological studies were also within normal range, including NBT test (Table 1).

**Table 1**

IgG: 1250 (441-1135)	CD8 (+): 19% (14-33%)
IgA: 114 (22.159)	CD4/CD8: 1.26 (0.9-2.9)
IgM: 422 (47-200)	CD19 (+): 32% (12-44%)
CD4 (+): 24% (23-48%)	CD3 (+): 25% (43-76%)

No pathogens were isolated on blood cultures although numerous acid-fast bacilli were observed on cervical secretion, sputum and gastric aspirate samples. Bacille Calmette-Guérin (BCG) was cultured from cervical secretion, sputum, gastric aspirated, pleural fluid and bronchial aspirate. The BCG bacilli were susceptible to rifampin, streptomycin, ethambutol and all second line antituberculous agents but resistant to isoniazid and pyrazinamide.

The possibility of a primary immunodeficiency due to a defect of the Interleukin-12 (IL-12)/Interferon (IFN  $\gamma$ ) pathway was suspected. Serum determination of IFN  $\gamma$  (by ELISA) showed low levels as well as the IFN  $\gamma$  secretion of stimulated peripheral blood mononuclear cells. Additional studies are on progress.

With these findings, our patient was diagnosed with disseminated BCG disease secondary to a defective IL-12 dependent IFN  $\gamma$  pathway. A daily regimen of rifampin, amikacin, ciprofloxacin and amoxicillin/clavulanate was initiated, and therapy with IFN  $\gamma$  (50mgm<sup>2</sup>, 3 times/week) was used as adjuvant treatment.