Partial Autosomal Dominant STAT-1 deficiency: A case series

Zacharoula Oikonomopoulou MD[1], Elizabeth P. Sampaio MD PhD [2], Alexandra Freeman, MD [2], Lily Blair, PhD[4], Asim Ahmed MD[4], Steven M. Holland, MD [2], Ben Z. Katz, MD[1, 3]

[1]Ann & Robert H Lurie Children's Hospital of Chicago, Division of Infectious Diseases
[2] National Institutes of Health
[3]Northwestern University, Feinberg School of Medicine, Department of Pediatrics
[4]Karius, Inc, Redwood City, CA, USA

Introduction

- The signal transducer and activator of transcription 1 factor (STAT1) plays a key role in the immunity against viral infections and mycobacteria
- Complete loss of function results in fatal infections during early childhood, while partial defects display milder clinical phenotypes
- Affected individuals may have a normal life span with the only infectious risk being recurrent infections with mycobacteria

Aim

- We describe a previously healthy 6 year-old girl who presented with 19 days of fevers and chills and her father
- This report will lead to a better understanding of the pathophysiology of the partial autosomal dominant STAT-1 deficiency and to its increased recognition

Methods

- Blood samples (5 mL) were collected in BD vacutainer plasma preparation tubes. Within 1 hour of sample collection, tubes were spun down at 1,100 RCF for 10 min at room temperature. Samples were shipped overnight to Karius, Inc. and measurement of cell free (cf) DNA using next generation sequencing (NGS) followed
- Blood samples from both parents and patient were collected and sent to the NIH for flow cytometry, cytokine assays, mutation analysis and gene expression/RT PCR analysis

Results (1)

- Patient is a previously healthy 6 year old girl who presented for evaluation of 19 days of fever at an outpatient ID clinic
- Patient had fatigue and decreased appetite and developed a fever to 38.8 ℃ that didn't have any specific pattern

ROS: No headache, visual changes, respiratory symptoms, nausea/emesis, abdominal pain, constipation, diarrhea, rash, joint swelling, warmth, erythema or pain

Social history: air travel to Washington DC with return 2 days prior to illness onset and a family visit to a farm 2 weeks after the illness began. There was no hiking and no known sick contacts, no travel outside the country, no exposure to undercooked meat, no eating of raw seafood, and no known tick bite, although she had some mosquito bites

Results (2)

Past medical history: Non-contributory

Family history: 40-year-old father who at age 18 developed a liver abscess with involvement of the spleen and lymph nodes due to *Mycobacterium avium complex* (MAC) diagnosed via liver biopsy. He had another MAC infection 5 years later. Following a year of therapy with ethambutol, rifampin and azithromycin, he was placed on weekly azithromycin prophylaxis; while on azithromycin he has had no other infectious complications. Initially diagnosed with a STAT-1 gain of function mutation. Interferon gamma receptor studies were normal.

Physical examination revealed a well-nourished, well-appearing girl. Temperature was 39.2°C, pulse 156, BP 111/70 mmHg and RR 24 breaths/minute. Lung exam was normal and abdominal exam was negative for hepatomegaly, splenomegaly or other palpable masses.

Significant laboratory studies

WBC 3.57 thou/uL, ANC of 1.110 thou/uL

Hgb 10.3 g/dL, PLT count 246 thou/uL

elevated CRP (1.9 mg/dL; normal <0.8 mg/dL)

elevated ESR (62 mm/hr; normal <20 mm/hr).

The following tests were negative or normal: CMP, coagulation panel, respiratory viral panel, adenovirus-specific nasopharyngeal swab PCR, monospot test, CMV IgG/IgM, *Bartonella henselae* and *B. quintana* IgG/IgM, ferritin, uric acid, HIV-1/2 Ab/Ag, NK cell function, total IgG, IgM, IgA.

- A blood next generation sequencing test (Karius test) revealed MAC after three days; see Figure 1

- A blood mycobacterial culture also resulted positive for MAC after 47 days.

Imaging

CXR: unremarkable

Abdominal U/S: incidental splenic hemangioma (2.8 cm) and moderate left kidney pelviectasis.

CT chest/abdomen/pelvis with contrast: incidental finding of moderate left hydronephrosis with a 4 mm non-obstructing calculus

Whole-body MRI without contrast: negative for bony involvement.

Therapy

-Initiated on clarithromycin, ethambutol and rifampin.

-Fevers resolved after 40 days; activity and appetite also returned to normal.

-CRP normalized within one month and ESR returned to normal within 6 months.

-Antibiotic therapy with clarithromycin, ethambutol and rifampin continued for one year and then she was initiated on azithromycin prophylaxis with no recurrence to date.

Figure 1.

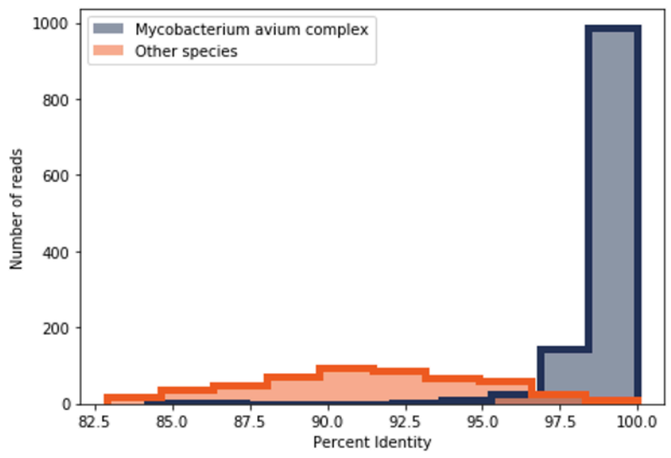

Figure 1A. *The histogram plot shows the percent identity of reads that align to Mycobacterium avium complex reference sequences. The blue bars denote the percent identity of reads to Mycobacterium avium complex and the orange bars represent the percent identity of the alignments to other species (distinct from Mycobacterium avium complex).*

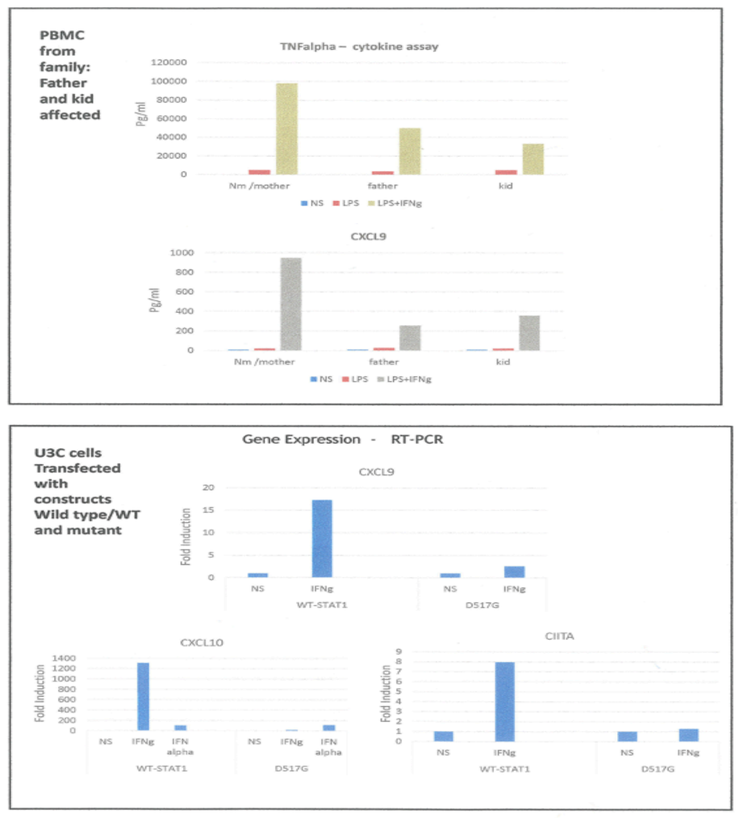

Figure 1B. *Cytokine assays revealed decreased responses of tumor necrosis factor alpha (TNFα), a target gene of IF-γ, in the peripheral blood mononuclear cells from the girl and her father following stimulation with lipopolysaccharide and IFγ (Fig 2, top), as expected. CXCL9 and CXCL10 are target genes of IF-γ; there was decreased gene expression of CXCL9 and CXCL10 following stimulation with IFγ, also as expected.*

Conclusions

- Partial STAT-1 deficiency is part of a well described group of gene mutations that are associated with Mendelian susceptibility to mycobacterial disease (MSMD)
- This clinical entity has a mild clinical phenotype. Other than increased susceptibility to mycobacterial and in some cases viral infections, these patients are generally healthy
- Partial dominant STAT-1 deficiency should be considered in patients presenting with isolated extrapulmonary mycobacterial infections

References

1. Rosain J, Kong X, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, Okada S, Boisson-Dupuis S, Casanova J, Bustamante J. Mendelian susceptibility to mycobacterial disease: 2014–2018 update Immunol Cell Biol. 2018; 1-8. doi:10.1111/imcb.12210
2. Sampaio EP, Bax HI, Hsu AP, *et al*. A novel STAT 1 mutation associated with disseminated mycobacterial disease. J Clin Immunol 2012; 32:681-9
3. Bustamante J,Boisson-Dupuis S,Abel L,Casanova JL.Mendelian susceptibility to mycobacterial disease:genetic, immunological, and clinical features of inborn errors of IFN-γ immunity.Semin Immunol. 2014;26(6):454-70
4. Cottle LE. Mendelian susceptibility to mycobacterial disease. Clin Genet 2011; 79:17-22. Doi: 10.1111/j.1399-0004.2010.01510.x

21st ICHS Symposium on
Infections in the Immunocompromised Host