

A Patient with Tyrosine Kinase 2 Deficiency without Hyper-IgE Syndrome

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We describe a Turkish patient with tyrosine kinase 2 deficiency who suffered from disseminated Bacille Calmette-Guerin infection, neurobrucellosis, and cutaneous herpes zoster infection. Tyrosine kinase 2 deficiency should be considered in patients susceptible to herpes viruses and intramacrophage pathogens even in the absence of atopy, high serum IgE, and staphylococcal disease. (*J Pediatr* 2012; ■: ■-■)

The first patient with autosomal recessive (AR) tyrosine kinase 2 (Tyk2) deficiency was reported in 2006.¹ That patient, a 22-year-old Japanese man, experienced multiple episodes of staphylococcal disease. Despite the lack of developmental defects typical of hyper-IgE syndrome (HIES), a diagnosis of HIES was proposed because the patient also had severe atopic dermatitis and an elevated serum IgE concentration (2100 IU/mL).¹ In 2007, mutations in *STAT3* were shown to be a cause of the common autosomal dominant (AD) form of HIES.² In addition to the recurrent staphylococcal infections of the skin and lungs, atopic dermatitis, and high serum IgE concentration (>1000 IU/mL) found in almost all patients with HIES, patients with AD HIES also display skeletal, dental, and connective tissue abnormalities.³ In contrast, the Japanese patient with Tyk2 deficiency had no bone fractures, and his dentition and facial appearance were normal. In addition to cardinal features of HIES, he presented with viral infections, including molluscum contagiosum and herpes simplex infections of the skin and mucosa. Such infections are seen in another form of AR HIES, which is due to mutations in *DOCK8*.⁴ Moreover, the patient had a history of Bacille Calmette-Guerin (BCG) disease at age 22 months and nontyphoidal *Salmonella* gastroenteritis at age 15 years, neither of which is typically associated with HIES.¹

We report here the clinical features of a different patient with Tyk2 deficiency. Despite some overlap, our patient and the Japanese patient with Tyk2 deficiency have markedly different clinical presentations.

Case Report

This 8-year-old male patient was first admitted in 1992 as a 2-year-old to Uludag University Hospital with fever, fatigue, and recurrent draining cervical, inguinal, and axillary lymph

nodes. He was born in 1992 and was the third child of healthy, first-cousin parents. The patient was vaccinated with BCG vaccine at age 2 months. At 8 months, left axillary lymphadenopathy was detected, and treatment with isoniazid was initiated. Although initially the regional lymphadenopathy began to regress, the patient developed generalized lymphadenopathy and fatigue at age 21 months. On admission, physical examination revealed fever (39°C) and fistulous enlarged bilateral lymphadenopathy in the cervical, axillary, and inguinal regions (Figure). Complete blood count and renal and hepatic function test results were normal. Intradermal skin tests with 5 tuberculin units purified protein derivative was negative. Chest X-ray showed no lung involvement, and a skeletal X-ray survey was normal. Immunologic assessments, including serum IgG, IgM, and IgA levels and nitroblue tetrazolium test results, were normal. Serum IgE concentration was 115 IU/mL (normal range, 1.2-52 IU/mL) (Table). Histological examination of his left axillary lymph node revealed widespread macrophage and polymorphonuclear cell infiltration in the dermis with positive staining for acid-fast bacilli. *Mycobacterium bovis* BCG was isolated from the discharging cervical sinuses.

The patient was treated with a regimen of isoniazid, rifampicin, streptomycin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for 16 months. His clinical condition improved, with no relapse.

At 8 years, the patient was admitted to a local hospital with a history of 12 hours of fever, generalized clonic-tonic seizure, frontal headache, and vomiting. At initial presentation, the patient was conscious. He had a temperature of 38.6°C, with no physical complaints except neck stiffness. He had a history of consuming unpasteurized cheese. A lumbar puncture performed on admission showed 200 cells/μL, with a predominance of polymorphonuclear leukocytes (80%). Blood and cerebrospinal fluid cultures were positive

AD	Autosomal dominant
AR	Autosomal recessive
BCG	Bacille Calmette-Guerin
HIES	Hyper IgE syndrome
IFN-γ	Interferon gamma
IL	Interleukin
Tyk2	Tyrosine kinase 2

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Figure. The patient had generalized, bilateral, cervical, axillary, and inguinal lymphadenitis on admission.

for *Brucella* spp. Brucellar agglutinins were detected to a dilution of 1/640, and tests for nonagglutinating antibodies (Coombs test) were positive. The patient received intramuscular streptomycin, oral rifampicin, and trimethoprim-sulfamethoxazole for 6 weeks.

Table. Immunologic parameters of the patient

	Patient at age 2 years	Normal value
Absolute lymphocyte count, /mm ³	4300	1100-5900
Absolute eosinophil count, /mm ³	296	50-350
IgG, mg/dL	1220	764-2134*
IgM, mg/dL	234	69-387
IgA, mg/dL	79.9	70-303
IgE, IU/mL	115	1.2-52
T cells, CD3 ⁺ , % (absolute count/mm ³)	67 (2881)	55-78 (700-4200)
B cells, CD19 ⁺ , % (absolute count/mm ³)	11 (473)	10-31 (200-1600)
CD4 ⁺ cells, % (absolute count/mm ³)	38 (1634)	27-53 (300-2000)
CD8 ⁺ cells, % (absolute count/mm ³)	22 (946)	19-34 (300-1800)
Natural killer cells, CD3 ⁺ CD16 ⁺ CD56 ⁺ , % (absolute count/mm ³)	20 (860)	4-26 (90-900)
Antibody response to tetanus toxoid, IU/mL	0.69	2-20
Nitroblue tetrazolium test, %	100	100

Ig, immunoglobulin.

*The normal serum Ig concentrations for age were defined according to reference values for healthy Turkish children.

A month after completion of treatment, the patient was admitted to our hospital because his parents reported hearing loss and inarticulate expression. The patient was uncooperative and aggressive. Physical examination disclosed severe cognitive impairment and pneumonia. X-ray and computed tomography scan of the chest revealed right pulmonary infiltration, but no abscess. Cefuroxime and clindamycin were administered for 10 days. A magnetic resonance imaging scan demonstrated lacunar infarcts in the left temporal and occipital lobes associated with both parietal lobes. Electroencephalography was normal. Audiometric results were 92 dB in the right ear and 82 dB in the left ear, demonstrating severe hearing loss (normal range, 10-15 dB). The patient refused to use a hearing aid because of his mental condition.

At age 11 years, the patient was hospitalized with herpes zoster of the right maxillary branch of the trigeminal nerve. At this time, he weighed 50 kg (95th percentile) and was 149 cm tall (75th percentile). The vesicles contained clear fluid and continued to increase in size over several days. The cornea was not involved at any stage. A 2-week course of intravenous acyclovir (30 mg/kg) was administered.

The clinical features of BCG disease were consistent with a defect in the interferon gamma (IFN- γ) pathway, and thus further in vitro investigations were performed. AR Tyk2 deficiency was diagnosed at age 17 years. The patient is homozygous for a 9-bp deletion in exon 16 of *TYK2*, c.2302_2310del or 2302del9, which creates a premature termination codon at position 767. As a result, there is no full-length Tyk2 protein detectable by Western blot analysis in Epstein-Barr virus-B cells. The detailed immunologic investigation of this patient, and its comparison with the Japanese patient, will be reported elsewhere.¹ Once Tyk2 deficiency was diagnosed in this patient, we looked for skeletal and dental manifestations of HIES, but all investigations were negative. Moreover, the patient's medical history contained no evidence of atopy, asthma, or skin problems such as candidiasis, boils, folliculitis, or cold abscess. Serum IgE concentration was measured at age 2, 11, 16, and 18 years and found to be normal or slightly high (80, 115, 218, 155 IU/mL, respectively), but well below the elevated level reported in the Japanese patient with Tyk2 deficiency (2100 IU/mL). The patient has developed no unusual infection in the last 6 years and is now 18 years old and off all treatment, but his social life is very limited because of developmental challenges and deafness.

The Institutional Review Boards of Uludag University, Necker Medical School, and Rockefeller University reviewed the informed consents of the patient and family members participating in the study.

Discussion

The patient with Tyk2 deficiency described by Minegishi et al¹ presented with relatively mild BCG disease but invasive nontyphoidal salmonellosis, probably due to impaired interleukin (IL)-12 (and possibly IL-23) responses. Our patient also suffered from disseminated BCG infection and

neurobrucellosis. Disseminated disease occurs in 1-3.4 children per million infants vaccinated. It usually occurs within 6 months of vaccination and is associated with a high case-fatality ratio of 80%-83%.⁵ Neurobrucellosis is uncommon and may take diverse forms, including encephalitis, meningoencephalitis, radiculitis, myelitis, and peripheral and cranial neuropathies.⁶ Neurobrucellosis caused severe neurological sequelae including sensorineural hearing loss and cognitive impairment in our patient. Tyk2 deficiency probably contributed to the occurrence of neurobrucellosis in this patient as a previous case of brucellosis and impairment of the IL-12–interferon (IFN)- γ circuit has been reported previously.⁷

IFN- γ is a key cytokine in the generation and regulation of the cellular immune response required to eliminate intracellular pathogens from macrophages. The absence of Tyk2 thus resulted in defective IL-12 signaling, leading to impaired IFN- γ production and susceptibility to BCG and *Brucella*.⁸ These infections by intramacrophagic bacteria are not seen in most patients with *STAT3* or *DOCK8* mutations and AD or AR HIES.

Molluscum contagiosum and herpes simplex virus caused skin and mucosal disease in the Japanese patient. Our Turkish patient developed herpes zoster infection of the maxillary branch of the trigeminal nerve, which was cured by 14 days of acyclovir treatment and did not recur. These viral illnesses were likely related to an impaired cellular response to IFN- α/β ,⁹ and have not been reported in patients with AD HIES. In patients with *DOCK8* deficiency, the viral illnesses occur through other mechanisms, involving a profound T-cell deficit.¹⁰ Neither patient with Tyk2 deficiency had coarse facial features or fragile bones, or any of the developmental features typically seen in patients with AD HIES.¹ However, unlike the Japanese patient with Tyk2 deficiency, our patient displayed none of the other 3 cardinal features of HIES: atopic dermatitis and eczema, staphylococcal infections of the skin and lung, or high serum IgE concentrations. His highest recorded IgE concentration was 218 IU/mL, at the age of 16 years.

The surprising discrepancy between the 2 clinical phenotypes is difficult to explain, but might result from a difference in the immunologic impact of Tyk2 in the 2 patients. In any case, a diagnosis of Tyk2 deficiency should be contemplated in patients with BCG clinical disease, particularly in the presence of unusually severe herpes virus

infections, even in the absence of cardinal features of HIES. This also may apply to patients with other mycobacterial diseases, whether tuberculous or atypical, as well as infections caused by other intramacrophage pathogens, such as *Salmonella* and *Brucella*. ■

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References

1. Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2006;25:745-55.
2. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of *STAT3* cause hyper-IgE syndrome. *Nature* 2007;448:1058-62.
3. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. *STAT3* mutations in the hyper-IgE syndrome. *N Engl J Med* 2007;357:1608-19.
4. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (*DOCK8*) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol* 2009;124:1289-302.
5. Filipe-Santos O, Bustamante J, Chappier A, Vogt G, de Beaucoudrey L, Feinberg J, et al. Inborn errors of IL-12/23- and IFN- γ -mediated immunity: molecular, cellular, and clinical features. *Semin Immunol* 2006;18:347-61.
6. Demiraslan H, Metan G, Mese EA, Yildiz O, Aygen B, Sumerkan B, et al. Neurobrucellosis: an evaluation of a rare presentation of brucellosis from a tertiary care center in Central Anatolia, Turkey. *Trop Doct* 2009;39:233-5.
7. Fieschi C, Dupuis S, Catherinot E, Feinberg J, Bustamante J, Breiman A, et al. Low penetrance, broad resistance, and favorable outcome of interleukin-12 receptor $\beta 1$ deficiency: medical and immunological implications. *J Exp Med* 2003;197:527-35.
8. Watford WT, O'Shea JJ. Human tyk2 kinase deficiency: another primary immunodeficiency syndrome. *Immunity* 2006;25:695-7.
9. Jouanguy E, Zhang SY, Chappier A, Sancho-Shimizu V, Puel A, Picard C, et al. Human primary immunodeficiencies of type I interferons. *Biochimie* 2007;89:878-83.
10. Randall KL, Chan SS, Ma CS, Fung I, Mei Y, Yabas M, et al. *DOCK8* deficiency impairs CD8 T cell survival and function in humans and mice. *J Exp Med* 2011;208:2305-20.