

(internal autoinoculation), or may be transferred from the fingers of an infected person (external autoinoculation).

The diagnosis of neurocysticercosis is confirmed by means of neuroimaging (CT and MRI) and serologic analysis. The enzyme-linked immunoelectrotransfer blot has a sensitivity and specificity of more than 98% and is the serologic assay of choice for the detection of cysticercosis.² Detection of the parasite in a biopsy specimen of skin nodules may also aid in the diagnosis. Cysticidal treatment is complicated by the fact that it initiates an inflammatory response that may precipitate seizures.³ However, a recent randomized, placebo-controlled trial showed a reduction in the rate of generalized seizures among the patients treated with albendazole.⁴ Corticosteroids are the primary form of therapy for cysticercotic encephalitis, angitis, and arachnoiditis.⁵ Although corticosteroids are recommended in conjunction with anthelmintic treatment to prevent an inflammatory response, the dose, duration, form, and — most important — timing of this treatment still remain controversial.

The diagnosis of neurocysticercosis should be suspected in all visitors and immigrants from Asia, South America, and Central America who have adult-onset epilepsy. In the case of native Americans with this form of epilepsy, asking whether they have a household worker from a country where the infection is endemic may provide a clue.

Igor Mamkin, M.D.

Nitesh Sood, M.D.

Sundaram V. Ramanan, M.D.

University of Connecticut Health Center

Farmington, CT 06030

igor_mamkin@yahoo.com

1. Garcia HH, Gonzalez AE, Evans CAW, Gilman RH. *Taenia solium* cysticercosis. *Lancet* 2003;362:547-56.
2. Scheel CM, Khan A, Hancock K, et al. Serodiagnosis of neurocysticercosis using synthetic 8-kD proteins: comparison of assay formats. *Am J Trop Med Hyg* 2005;73:771-6.
3. Carpio A. Neurocysticercosis: an update. *Lancet Infect Dis* 2002;2:751-62.
4. Garcia HH, Pretell EJ, Gilman RH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004;350:249-58.
5. Garcia HH, Evans CAW, Nash TE, et al. Current consensus guidelines for treatment of neurocysticercosis. *Clin Microbiol Rev* 2002;15:747-56.

STAT3 Mutation in the Original Patient with Job's Syndrome

TO THE EDITOR: In 1966, a report on two unrelated young girls who had had recurrent staphylococcal abscesses since infancy was introduced with the biblical quote, "So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown" (Job 2:7).¹ The authors called this disorder the Job syndrome because of the phenotypic similarity to the biblical figure Job. Subsequently, similar patients were recognized and noted to have markedly elevated IgE levels, leading to the name "hyper-IgE syndrome" (HIES). (Details about the second girl, who died at the age of 19 years, are provided in the Supplementary Appendix, available with the full text of this letter at www.nejm.org.)

The cause of the syndrome remained elusive until 2006, when a homozygous mutation in the tyrosine kinase 2 (TYK2) gene was discovered in a patient with a variant form of HIES, which suggested that defects in signaling between Janus kinase (JAK) and signal transducer and activator of transcription (STAT) may cause the Job syndrome.² We and other investigators^{3,4} have recently identified heterozygous hypomorphic mutations in

the *STAT3* gene in a majority of patients with the classic autosomal dominant form of Job's syndrome.

The protocol for our research was approved by the institutional review board at the University of Washington School of Medicine and Children's Hospital, Seattle. All subjects in the study provided written informed consent.

One of the two original patients with the Job syndrome¹ remains alive in our cohort of patients with classic HIES. This patient (Subject II-3),¹ who is now 50 years of age, has had lifelong eczema, multiple atraumatic fractures, hyperkeratotic fingernails owing to candida infection, recurrent *Staphylococcus aureus* abscesses, and pneumonia with lung abscesses and formation of pneumatoceles. She gave birth to three boys by two fathers (Fig. 1). Her first son (Subject III-1) died 3 days after birth from pneumonia and sepsis with *Pseudomonas aeruginosa* and acinetobacter. Her second son (Subject III-3) was hospitalized shortly after birth with *S. aureus* pneumonia. Later, eczema developed, along with rising IgE levels (104,000 IU per milliliter in his second year of life [normal value, <64]),

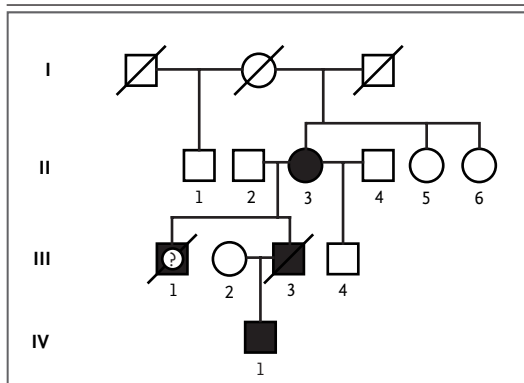


Figure 1. Pedigree of the Original Patient.

The original patient with Job's syndrome (Subject II-3) was first described by Davis et al.¹ in 1966. Squares indicate male subjects, and circles female subjects. Solid symbols indicate affected subjects, open symbols unaffected subjects, and symbols with a slash deceased subjects. Patient III-1 died at 3 days of age with sepsis and pneumonia and presumably was affected.

multiple skin abscesses, candidiasis, pneumonia with formation of pneumatoceles, and spontaneous rib fractures; he also retained his primary teeth. At 28 years of age, he underwent lobectomy because of multiple pneumatoceles and persistent *S. aureus* and aspergillus infections. He died at the age of 29 years from respiratory failure. His 8-month-old son (Subject IV-1) was hospitalized at 3 months of age with failure to thrive, pneumothorax, *S. aureus* pneumonia with abscess formation, empyema, and multiple rib fractures. His current IgE level is 45 IU per milliliter (normal value, <15).

Mutation analysis of the *STAT3* gene revealed a heterozygous point mutation in exon 12 (1144C→T; protein, R382W) in the index patient and her two

affected descendants (Subjects III-3 and IV-1). R382W is not reported as a single-nucleotide polymorphism and was not observed in the unaffected relatives of the index patient (Subjects II-1, II-2, II-5, II-6, III-2, and III-4) or in 200 ancestrally matched chromosomes.

Arginine at position 382 is highly conserved and directly involved in DNA binding.⁵ This amino acid substitution is the most common *STAT3* mutation identified in classic autosomal dominant HIES. It accounts for nearly half the identified mutations.^{3,4} Since all these mutations are hypomorphic (missense mutations or in-frame deletions) and involve only one allele of *STAT3*, this finding suggests a dominant negative effect.

Ellen D. Renner, M.D.

Troy R. Torgerson, M.D., Ph.D.

Stacey Rylaarsdam, A.A.A.S.

Stephanie Añover-Sombke, B.S.

Karin Golob

Taylor LaFlam

Qili Zhu, M.D.

Hans D. Ochs, M.D.

University of Washington School of Medicine

Seattle, WA 98195

allgau@u.washington.edu

1. Davis SD, Schaller J, Wedgwood RJ. Job's syndrome: recurrent, "cold," staphylococcal abscesses. *Lancet* 1966;1:1013-5.

2. Minegishi Y, Saito M, Morio T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2000; 25:745-55.

3. Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of *STAT3* cause hyper-IgE syndrome. *Nature* 2007;448:1058-62.

4. Holland SM, DeLeo FR, Elloumi HZ, et al. *STAT3* mutations in the hyper-IgE syndrome. *N Engl J Med* 2007;357:1608-19.

5. Becker S, Groner B, Müller CW. Three-dimensional structure of the *Stat3* homodimer bound to DNA. *Nature* 1998;394:145-51.

Correspondence Copyright © 2007 Massachusetts Medical Society.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following: •Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at <http://authors.nejm.org>. •A letter can have no more than five references and one figure or table. •A letter can be signed by no more than three authors. •Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the published articles.) •Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: <http://authors.nejm.org>

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Renner ED, Torgerson TR, Rylaarsdam S, et al. *STAT3* mutation in the original patient with Job's syndrome. *N Engl J Med* 2007;357:1667-8.

Second Job Syndrome patient

A second female patient was described in the initial report of Job syndrome (case #2)¹. This patient died of chronic lung disease at age 19. She had no offspring and was the only affected member in her family which has been lost to follow up.

Methods

Mutation Analysis

Mutation analysis was performed on cDNA and confirmed by genomic DNA sequencing for members of this cohort. To prepare cDNA, total mRNA was extracted from 5×10^6 fresh peripheral blood mononuclear cells (PBMC) using Trizol reagent (Invitrogen, Carlsbad, CA) and subjected to first strand cDNA synthesis using the Omniscript RT Kit (Qiagen, Valencia, CA) per the manufacturer's protocols. Genomic DNA was prepared from buffy coats of heparinized blood samples using the QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA) according to the manufacturer's protocol. The *STAT3* gene was amplified from cDNA or gDNA using specific oligonucleotide primers and polymerase chain reaction. The amplified gene fragments were sequenced using the ABI Big Dye Terminator mix (Applied Biosystem, Foster City, CA), and analyzed with a 3730xl DNA Analyzer (Applied Biosystem, Foster City, CA). Mutations were reported using the nomenclature of den Dunnen and Antonarakis².

Oligonucleotide primer sequences

The *STAT3* cDNA was amplified and sequenced in two fragments using the following primer sets: F 5'-AACCGGATCCTGGACAGGCA-3' / R 5'-AGCTCCTCAGTCACAATCAG-3' and F 5'-GGAAGAATCCAACAACGGCA-3' / R 5'-GGAGGCACTTGTCTAAGAAC-3'. Exon 12 of the *STAT3* gene was amplified and sequenced from gDNA using the following primer set: F 5'-GGACGTTGCAGCTCTCAGAGG-3' / R 5'-CTGCAGAGAGGCTGCCGTTG-3'.

References

1. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet* 1966;1:1013-5.
2. den Dunnen JT, Antonarakis SE. Nomenclature for the description of human sequence variations. *Hum Genet* 2001;109:121-124.