Korean Journal of Pediatrics Vol. 53, No. 4, 2010
DOI : 10.3345/kjp.2010.53.4.592
■ Case report ■

A case of Hyper-IgE syndrome with a mutation of the STAT3 gene

Ji-man Kang, M.D.[*], Jungmin Suh, M.D.[*], Jihyun Kim, M.D.[†], Hee-Jin Kim, M.D., Ph.D.[‡], Yae-jean Kim, M.D.[*], Hun Seok Lee, M.S.[§], Young Kee Shin, M.D., Ph.D.[§], Kangmo Ahn M.D., Ph.D.[*], and Sang-Il Lee, M.D., Ph.D.[*]

Department of Pediatric[*], Samsung Medical Center, Sungkyunkwan University School of Medicine, Department of Pediatrics[†], College of Medicine, Chung-Ang University, Seoul
Department of Laboratory Medicine & Genetics[‡], Samsung Medical Center, Sungkyunkwan University School of Medicine, the Research Institute of Pharmaceutical Science, Seoul
Seoul National University College of Pharmacy[§], Seoul, Korea

= Abstract =

Hyperimmunoglobulin E syndrome (HIES) is a rare immunodeficiency disease which is characterized by high serum IgE levels, eczema, and recurrent infections. Herein we present the case of a patient with HIES associated with STAT3 gene (*stat3*) mutation. A 16 year-old girl was admitted to our hospital due to hemoptysis caused by pneumonia with bronchiectasis. She had a history of recurrent skin and respiratory tract infections, such as pneumonia caused by MRSA (methicillin-resistant *Staphylococcus aureus*) and *Pseudomonas aeruginosa*. On physical examination, a broad round shaped nose, oral thrush, and chronic eczematous skin rash over her whole body were found. Laboratory data showed an elevated eosinophil count (750/μL) and total IgE level (5,001 U/mL). The patient's National Institutes of Health (NIH) score for HIES was 44. Direct sequencing of the STAT3 gene revealed that the patient was heterozygous for a missense mutation in the DNA binding domain of the STAT3 protein (c.1144C>T, p. Arg382Trp). HIES should be suspected in patients with recurrent infections and can be confirmed by clinical scoring and genetic analysis. **(Korean J Pediatr 2010;53:592-597)**

Key Words : Hyper IgE syndrome (HIES), Immunodeficiency, STAT3

Introduction

Hyperimmunoglobulin E Syndrome (HIES) is a rare immunodeficiency which is characterized by eczema, *Staphylococcus aureus* skin infections, pneumonia with abscess or pneumatocele formation, *Candida* infections, and skeletal and connective tissue abnormalities[1)].

In 1966, Davis et al. reported two patients with eczema, recurrent pneumonia, and "cold" skin abscesses. This disease entity was named as "Job syndrome", referring to the Biblical Job who had been "smitten with sore boils from the soles of his feet unto his crown" (Job 2:7)[2)]. Subsequently, as the patients with similar clinical findings were reported, additional characteristic abnormalities were found including distinct facial features, hyperextensible joints, pathologic bone fractures, scoliosis, craniosynostosis, and retained primary dentition. These patients also had markedly elevated serum IgE levels, which led to the disorder being named *hyper-IgE syndrome*[3)].

Because of the lack of a confirmative test, a clinical scoring system, known as NIH score, was suggested by Grimbacher et al. and has been used to screen HIES[4)]. Recently, several gene mutations responsible for HIES has been reported[5-7)]. In particular, mutations in the signal transducer and activator of transcription factor 3 gene (*stat3*) have been determined to be the cause of autosomal dominant HIES[5)].

In the Korean literature, HIES or Job syndrome has only been reported on the basis of clinical manifestations so far[8-15)]. Gene mutations have never been confirmed in any of these cases. Here we report a sporadic case of HIES

Received : 12 November 2009, Revised : 26 January 2010
Accepted : 18 February 2010
Address for correspondence : Kangmo Ahn M.D., Ph.D.
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University, School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel : +82.2-3410-3539, Fax : +82.2-3410-0043
E-mail : kmaped@skku.edu

who had characteristic symptoms with an NIH score of 44. Molecular genetic test revealed a missense mutation in the STAT3 gene, which was also confirmed by functional analysis.

Case report

A 16 year-old girl was admitted to our hospital due to hemoptysis. She was born full term without perinatal problems. However, she had a history of eczematous rash over her whole body in the neonatal period and a bowel perforation at 8 months of age. She also had a history of recurrent skin and respiratory tract infections such as skin abscess, otitis media, sinusitis and pneumonia. About 3 months prior to admission, she had been hospitalized twice due to pneumonia caused by *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively.

On physical examination, her body gauges were normal, but a broad round-shaped nose and oral thrush was found. Bronchial breath sounds and crackles were heard in the whole lung fields and aeration was decreased in the right lower lung field. She had chronic eczematoid skin rashes on the whole body (Fig. 1). Chest radiography and computed tomography (CT) revealed bronchiectatic changes in both lungs with right pleural effusion (Fig. 2). Laboratory tests revealed a WBC count of 15,530/μL, with elevated eosinophil count (750/μL) and strikingly high total IgE level (5,001 U/mL); C-reactive protein level (20.14 mg/dL) and erythrocyte sedimentation rate (120 mm/hr) were also highly elevated; The results of nitroblue tetrazolium test and lymphocyte subset analysis were normal (Table 1). Tuberculin skin test result was negative. Egg white- specific IgE was positive by MAST CLA Allergy test (Hitachi Chemical Diagnostics, CA, USA). MRSA was isolated from sputum

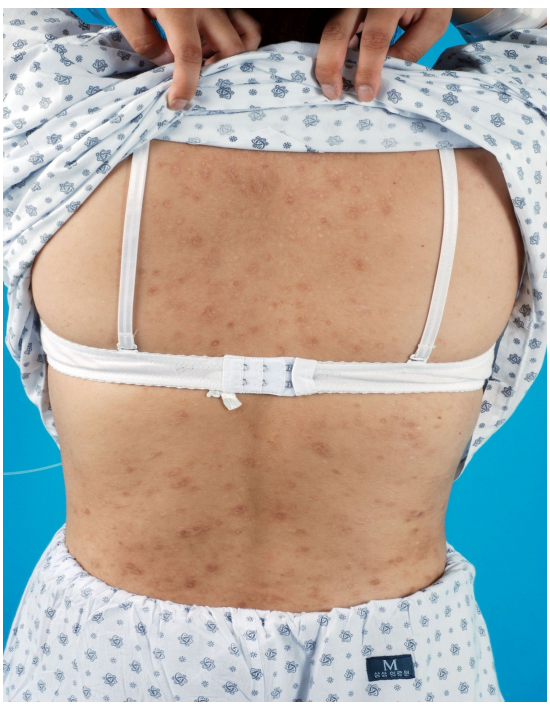

Fig. 1. Eczematoid skin rashes on the whole body.

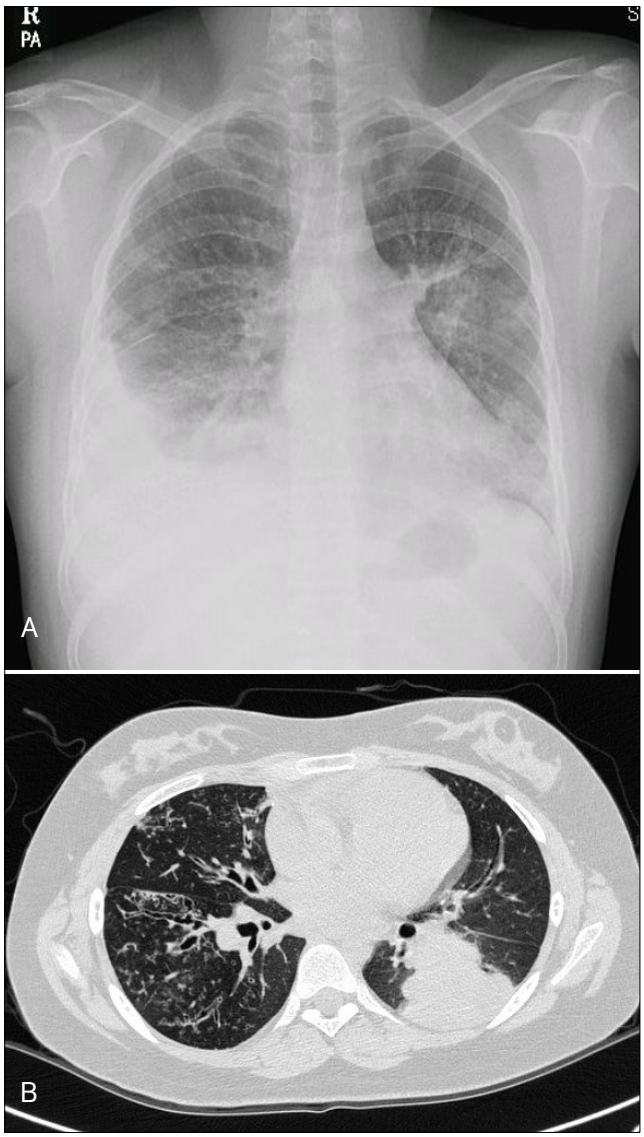

Fig. 2. (A) Chest radiography (B) Chest computed tomography (CT) scan showing both lower lobe pneumonia with underlying bronchiectatic change.

culture. The patient's National Institutes of Health (NIH) score was 44 (Table 2). Direct sequencing of the STAT3 gene was performed after informed consent obtained. It revealed a heterozygous missense mutation in the DNA binding domain of the protein (c.1144C>T, p. Arg382Trp) (Fig. 3). The patient was also found to have impaired generation of IL-17-secreting CD4+ T cells (T_H17 cells) on stimulation in flow cytometric analyses (Fig. 4). After antimicrobial treatment for 2 weeks, she recovered and was discharged with prophylactic bactrim and bleach bath education.

Table 1. Laboratory Data

Test	
Complete blood cell count	
Hb (g/dL)	9.8
WBC (/μL)	15,530
Segmented neutrophil (%)	63.6
Eosinophil count (/μL)	750
Platelet (/μL)	328,000
C-reactive protein (mg/dL)	20.14
Erythrocyte sedimentation rate (mm/hr)	120
Anti-mycoplasma antibody	positive (1:320)
Immunoglobulin level	
IgG (mg/dL)	2,533
IgA (mg/dL)	163
IgM (mg/dL)	268
IgE (IU/mL)	968
Lymphocyte subset	
T3	77% (2,490/μL)
T4	43% (1,390/μL)
T8	32% (1,030/μL)
T4/T8 ratio	1.34
B (CD19)	14% (460/μL)
NK (CD16+CD56)	9% (290/μL)
Nitroblue tetrazolium (NBT) test (%)	59
Tuberculin test	Negative
Allergen-specific IgE (MAST)	Egg white(+)

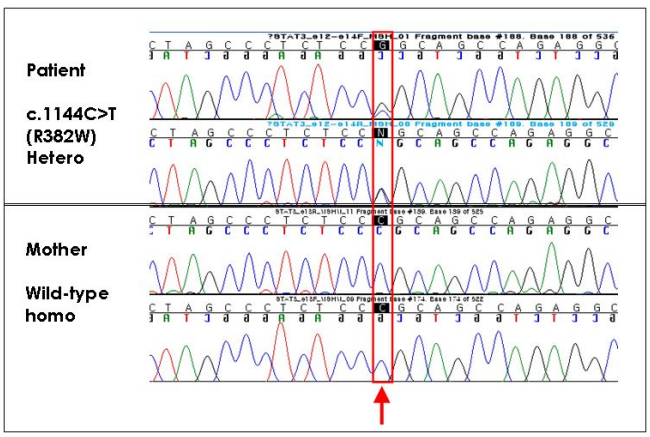

Fig. 3. Results of the direct sequencing analysis of *stat3*.

Table 2. National Institutes of Health Score for the Patient

Clinical findings＼Points	0	1	2	3	4	5	6	7	8	9	10
Highest serum IgE (IU/ml)	<200	200-500			501-1,000				1,001-2,000		>2,000*
Skin abscesses	None		1-2		3-4				>4*		
Pneumonia	None		1		2		3		>3*		
Parenchymal lung disease	Absent						Bronchiectasis*		Pneumoatocele		
Retained primary teeth	None*	1	2		3				>3		
Scoliosis	<10° *		10-14°		15-20°				>20°		
Fractures with minor trauma	None				1-2*				>2		
Highest eosinophil count	<700*			700-800			>800				
Characteristic face	Absent		Mildly*			Present					
Midline anomaly	Absent*					Present					
Newborn rash	Absent				Present*						
Eczema (worst)	Absent*	Mild	Moderate		Severe						
URI/year		3*	4-6		>6						
Candidiasis	None	Oral*	Fingernails		Systemic						
Other serious infections	None*				Severe						
Fatal infection	Absent*				Present						
Hyperextensibility	Absent*				Present						
Lymphoma	Absent*				Present						
High palate	Absent*		Present								
Young-age correction	>5yr*			2-5yr		1-2yr		≤1yr			

*shows the case of the patient

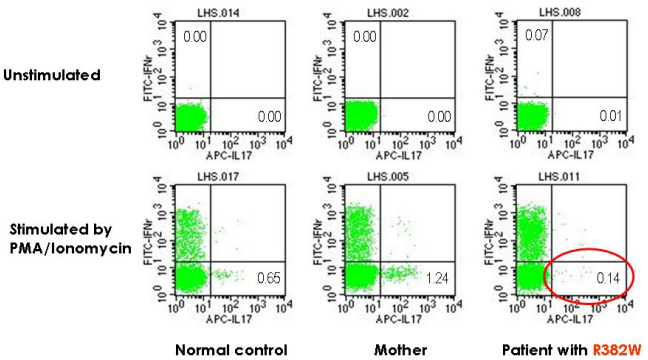

Fig. 4. Flow cytometric analysis of the IL-17 production by CD4+ T cells on stimulation.

Discussion

Most cases of HIES are sporadic. However, familial cases with autosomal dominant or autosomal recessive pattern of inheritance have also been described[16]. Although the pathogenesis of HIES remains unclear, gene mutations have been identified to be the cause of the disease[5, 7]. In particular, a heterozygous mutation in the STAT3 gene is known to be the predominant cause of sporadic and familial HIES, and the most of mutations reside within the DNA binding, SH2 and transactivation domains[5, 6, 17]. Recently, a homozygous mutation of tyrosine kinase 2 was discovered in a patient with eczema, moderately elevated serum IgE, and a mild T-cell deficiency[7]. However, some patients who was clinically diagnosed with HIES had no *stat3* mutations[6, 18], indicating further genetic heterogeneity of the disease. In our patient, we found R382W mutation of the DNA-binding domain, which was reported to be the most frequent *stat3* mutation in previous studies[5-7]. Recently, we also reported a novel missense mutation of STAT3 in a Korean boy with HIES, which was the first mutation to be found in the linker domain[19]. Our findings suggest that mutant STAT3 be the genetic background in a significant proportion of Korean patients with HIES, and thus, a molecular genetic study for *stat3* mutation is warranted to confirm the diagnosis as clinically indicated.

We observed that the stimulated $CD4^+$ T cells of our patient were severely defective of producing IL-17. This finding is consistent with those of the previous study that had shown *stat3* mutations resulted in impaired differentiation of IL-17-producing T_H17 cells[20]. Because IL-17 plays a major role in host defense mechanism, especially against extracellular bacteria and fungi, the deficiency of T_H17 cells may directly affect susceptibility to *S. aureus* and *Candida*. In the hematopoietic system, *stat3* mutations result in impaired neutrophil chemotaxis and eosinophilia by up-regulation of IL-4 and IL-5 and down-regulation of IFN-γ[21]. In addition, *stat3* knock out animal models also develop osteoporosis, because of enhanced osteoclastogenesis, and wound healing impairment by delayed keratinocytes migration[21, 22]. These bone and connective tissue abnormalities are one of the typical symptoms in HIES patients, who often present with bone fractures, retained neonatal teeth, cold skin abscesses and pneumatoceles after pneumonias.

At present, there is no specific treatment for HIES, so prevention with prophylactic antimicrobial agent is important. Baths in diluted bleach for 15 minutes three times weekly are helpful to control staphylococcal skin eruptions. Aggressive antimicrobial therapy should be done when necessary. Systemic immune suppression (eg, with corticosteroids) to treat the eczema usually is not required, but topical steroids do help in difficult cases. Antimicrobial prophylaxis to prevent *S. aureus* skin and lung infections (eg, 2.5 mg/kg of the trimethoprim component twice daily) may be used. Antifungal prophylaxis to prevent pulmonary aspergillosis remains attractive but so far has not demonstrated any measurable benefits. Ideally, treatment of pneumonia is guided by the etiologic agent. Additionally, the benefit of intravenous immunoglobulin[23], bone marrow transplantation[24], and bisphosphonates for treating the HIES-related osteoporosis are unclear.

In conclusion, HIES is not a common disease but should be considered in patients with chronic eczematous skin rashes accompanied by recurrent skin and respiratory infections. Medical history, careful physical examination and determination of serum IgE levels are essential in screening for HIES, and detection of *stat3* mutations is helpful for diagnosis and genotyping of HIES.

한 글 요 약

STAT3유전자 돌연변이 검사로 확진된 고면역글로불린E 증후군 1례

성균관대학교 의과대학 삼성서울병원 소아과학교실[*],
중앙대학교 의과대학 소아과학교실[†],
성균관대학교 의과대학 삼성서울병원 진단검사의학교실[‡],
서울대학교 약학대학[§]

**강지만[*] · 서정민[*] · 김지현[†] · 김희진[‡] · 김예진[*]
이훈석[§] · 신영기[§] · 안강모[*] · 이상일[*]**

고 IgE 증후군은 만성 습진성 피부병변, 반복적인 호흡기 감염과 고 IgE 혈증이 특징인 드문 면역결핍질환이다. 환아는 객혈을 주소로 내원한 16세 여아로, 과거력상 신생아시기서부터 시작된 반복적인 피부발진, 잦은 상기도 감염 및 폐렴으로 외부병원에서 지속적인 치료를 받은 바 있었다. 가족력 상에는 특별한 이상이 없었다. 신체검진상 전신의 만성 습진성 피부병변, 크고 뭉특한 코, 아구창 등을 관찰할 수 있었고, 청진상의 양폐야의 부잡음 및 우측 하엽의 호흡음이 감소되었다. 전신 흉부방사선 촬영상 양측 폐야의 기관지확장성 변화를 동반한 우하엽의 흉수 및 경화가 관찰되었으며, 말초혈액검사상 호산구수치(750/μL) 및 면역글로불린 E 수치(5,001 U/mL)가 증가되었다. 환아는 임상적으로 고 IgE 증후군이 의심되었으며, 유전자 검사를 통해 확진하였다(Arg382Trp). 최근의 연구에 따르면, 고 IgE 증후군의 주된 원인으로 STAT3 유전자의 이상이 알려져 있으며, 이를 유발하는 여러 돌연변이가 보고되어 있다. 저자들은 STAT3 유전자의 돌연변이 중 잘 알려진 Arg382Trp 돌연변이를 우리나라에서 최초로 유전자 검사를 통해 본 환아에게서 확진하였기에 문헌고찰과 함께 보고하는 바이다. 고 IgE 증후군은 만성 습진성 피부병변, 반복적인 호흡기 감염 등 특징적인 병력이 있는 환자에서 고 IgE 혈증이 동반될 때 임상적으로 의심할 수 있으며, 유전학 검사로 확진이 가능하다.

References

1) Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections: an autosomal dominant multisystem disorder. N Engl J Med 1999;340:692-702.
2) Davis SD, Schaller J, Wedgwood RJ. Job's syndrome: recurrent, "cold," staphylococcal abscesses. Lancet 1966;(7445):1013-5.
3) Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics 1972;49:59-70.
4) Grimbacher B, Schaffer AA, Holland SM, Davis J, Gallin JI, Malech HL, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet 1999;65:735-44.
5) 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.
6) Renner ED, Rylaarsdam S, Anover-Sombke S, Rack AL, Reichenbach J, Carey JC, et al. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced Th17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. J Allergy Clin Immunol 2008;122:181-7.
7) 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.
8) Park SK, Choi SJ, Kim YW. Hyperimmunoglobulin E (Job's) syndrome: case report. J Korean Radiol Soc 2003;48:323-6.
9) Min BJ, Shin JS, Lee IS, Shin YK. Pulmonary features of hyperimmunoglobulin E (Job's) syndrome. Tuberc Respir Dis 2002;52:651-6.
10) Lee SJ, Lee J, Park JH, Lee JH, Koo SW, Choi GS, et al. A case of Job's syndrome. Korean J Dermatol 2000;38:1382-4.
11) Jang KA, Suh CW, Choi JH, Sung KJ, Moon KC, Koh JK. Job's syndrome: suspected case. Korean J Dermatol 1999;37:407-9.
12) Min JK, Cho ML, Kim SC, Lee YS, Lee SH, Park SH, et al. Hyperimmunoglobulin E-recurrent infection syndrome in a patient with juvenile dermatomyositis. Korean J Intern Med 1999;14:95-8.
13) Sohn MH, Park KH, Jeong BJ, Kim KE, Lee KY. A case of Job syndrome-experience with thymopentin. Pediatr Allergy Respir Dis 1997;7:122-9.
14) Lim DH, Kim JH, Chang YJ, Kim SK, Son BK. A case of hyperimmunoglobuline E syndrome. J Korean Pediatr Soc 1993;36:119-25.
15) Shinn MC, Choi SD, Suh BG, Kang JH, Lee JS. A case of hyperimmunoglobulin E syndrome. J Korean Pediatr Soc 1991;34:292-8.
16) Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. Immunol Rev 2005; 203:244-50.
17) 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.
18) Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr 2004;144:93-9.
19) Kim HJ, Kim JH, Kwon MJ, Lee SI, Ahn KM. A novel mutation in the linker domain of STAT3 gene, p.Lys531Glu, in hyper-IgE syndrome. J Allergy Clin Immunol 2009;123:956-8.
20) Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 2008;452:773-8.
21) Chehimi J, Elder M, Greene J, Noroski L, Stiehm ER, Winkelstein JA, et al. Cytokine and chemokine dysregulation in hyper-IgE syndrome. Clin Immunol 2001;100:49-56.

22) Sano S, Itami S, Takeda K, Tarutani M, Yamaguchi Y, Miura H, et al. Keratinocytespecific ablation of STAT3 exhibits impaired skin remodeling, but does not affect skin morphogenesis. EMBO J 1999;18:4657-68.
23) Bilora F, Petrobelli F, Bocioletti V, Pomerri F. Moderate-dose intravenousimmunoglobulin treatment of Job's syndrome. Case report. Minerva Med 2000;91:113-6.
24) Nester TA, Wagnon AH, Reilly WF, Spitzer G, Kjeldsberg CR, Hill HR. Effects of allogeneic peripheral stem cell transplantation in a patient with Job syndrome of hyperimmunoglobulinemia E and recurrent infections. Am J Med 1998; 105:162-4.