The Rate of Pyrin Mutations in Critically Ill Patients with Systemic Inflammatory Response Syndrome and Sepsis: A Pilot Study

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ABSTRACT. ***Objective.*** The role of individual genetic differences in susceptibility to systemic inflammatory response syndrome (SIRS) and sepsis is generally unrecognized or underestimated. We investigated the rate of pyrin mutations in critically ill patients with SIRS and sepsis, and compared whether carriers for pyrin mutations are associated with respect to the frequency of and certain features of sepsis and SIRS.

Methods. We tested M694V, M680I, V726A, R761H, and M694I mutations in critically ill patients.

Results. Twenty-four of 80 (30%) critically ill patients were found to carry some pyrin mutations; none had a history compatible with familial Mediterranean fever. We also found a high frequency of carriers in patients having pneumonia (30.3%), urinary tract infection (29.4%), and acute pancreatitis (30.8%). When we compared our results with the pyrin mutation carrier rate of a healthy Turkish population (10%), the rate of pyrin mutations in all patients ($p < 0.001$), and patients with urinary tract infection ($p < 0.001$), acute pancreatitis ($p < 0.001$), and pneumonia ($p < 0.001$) were found to be significantly high. The white blood cell count, erythrocyte sedimentation rate, lactic dehydrogenase, and rate of fever and pulse were significantly higher, whereas systolic and diastolic blood pressure and albumin levels were significantly lower in patients with pyrin mutation compared to those without the mutation.

Conclusion. Our results showed that critically ill patients with SIRS and sepsis have increased prevalence of pyrin mutations, and patients with SIRS and sepsis carrying the pyrin mutation seem to be highly susceptible for a severe disease course. (First Release August 1 2007; J Rheumatol 2007;34:2070–4)

Key Indexing Terms:
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME — SEPSIS
PYRIN MUTATION — CRITICAL ILLNESS

The term systemic inflammatory response syndrome (SIRS) recognizes that in critical illness clinical inflammation can arise from infectious and noninfectious stimuli, for example, in cases of pancreatitis, polytrauma, or immune complex disease[1]. The pathophysiology of SIRS is characterized by changes that alter the crosstalk among the immune, endocrine, and other systems[2]. The SIRS denotes systemic inflammation, independent of its cause; when the cause is infection, the process is termed sepsis. The preponderance of research in sepsis has focused on dissecting the roles of the immune system cells, innate immune regulation, proinflammatory cytokines released from blood monocytes, and coagulation factors in response to varying infectious and inflammatory mediators[3]. In addition, the effects of genetic polymorphism on the severity and outcome of illness requiring critical care including sepsis and SIRS have been reported[4,5]. Various genes in each cascade reaction of sepsis have been assessed, including not only cytokines but also other genes in the septic pathway, or innate immunity through Toll-like receptor (TLR)4[6] or CD14[7], etc. Watanabe, *et al*[5] reported that interleukin 1 (IL-1)-related polymorphism appears to strongly influence cytokine production in and outcome of patients with SIRS or septic complications.

Familial Mediterranean fever (FMF) is a recessive disorder characterized by acute episodes of fever and neutrophil-mediated recurrent serosal inflammation[8]. The gene responsible for FMF, called *MEFV*, is located on the short arm of chromosome 16[9,10]. *MEFV* codes for a 781-amino acid protein, termed pyrin or marenostrin, and includes a PYRIN domain (PYD)[9-11]. PYD is one of the 3 domains for an antimicrobial triad[12]. *MEFV* is expressed predominantly in granulocytes and cytokine-activated monocytes[13], suggesting that pyrin plays some intrinsic role in regulating leukocyte function. To date more than 70 FMF gene mutations have been recorded[14]. Five founder molecular alterations, E148Q in exon 2 and M694V, M680I, M694I, and V726A in exon 10, account for about 80% of cases occurring in patients of Mediterranean ancestry[15].

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However, it is still ambiguous whether E148Q is a true FMF mutation or not. It has been described that the allele frequency of pyrin E148Q in healthy controls was relatively high, and some healthy individuals had a homozygous form of this mutation, therefore pyrin E148Q has been considered to be a normal variant[16,17]. The estimated prevalence of FMF in Turkey is 1/1000, and the carrier rate is 1:5[18-20]. Turks are one of 4 populations (the others being Jews, Armenians, and Arabs) who have a high carrier rate. These have been reported to have an overall carrier rate of 1:5 in a mixed Arabic population[21], 1:7 in Armenians[22], and 1:5 in Sephardic Jews[23]. Despite the high frequency of the carrier rate, the selective biological advantage or disadvantage, if any, for carriers of pyrin mutations is not known[24]. In this context, Kalyoncu *et al*[25] suggested that one pyrin mutation may indeed be conferring a heightened tendency to inflammation as indicated by the increased frequency in inflammatory symptoms[25]. They also hypothesized that the carrier status for pyrin mutations seems to cause an alteration in the state of health[25].

We aimed to investigate the rate of pyrin mutations in critically ill patients with SIRS and sepsis, and to compare whether carriers for the pyrin mutations have a tendency with respect to the frequency of certain features of sepsis and SIRS. We compared clinical and biochemical measures in patients with and without pyrin mutations.

MATERIALS AND METHODS

Eighty Turkish patients (47 women, 33 men, age range 40 to 65 yrs, median 56.46 ± 6.12 yrs) presenting with SIRS and sepsis at the intensive care unit of Gülhane Military Medical Academy were included. The underlying disorders of these patients were pneumonia (n = 33), urinary tract infection (n = 34), and acute pancreatitis (n = 13). Patients who had clinical diagnosis of FMF, homozygote for pyrin mutations, or positive family history of FMF were excluded. We evaluated and recorded body temperature, blood pressure, heart rate, respiratory rate, blood gas analysis, and white blood cell count (WBC) daily. Radiographic diagnostics and microbiological examinations were performed on admission in all patients and thereafter when indicated. Two blood cultures were performed on the admission day, then repeated if a patient's temperature was > 38°C, or they were under systemic steroid or immunosuppressive therapy.

Criteria for the diagnosis of pneumonia and urinary tract infection were derived from US Centers for Disease Control definitions[26,27]. Pneumonia was assessed according to daily chest radiograph, the presence of purulent tracheal aspirates containing microorganisms, and the results of bronchoalveolar lavage. Urine dipstick test, urine culture, tracheal aspirates or sputum and nasal secretion cultures, microbiological surveillance of drainage systems, and culture of removed catheters were performed systematically. Inclusion criteria for acute pancreatitis were as follows[28]: (1) SIRS; (2) initiation of a typical epigastric pain radiating to the back over the last 12 h before admission; (3) serum amylase at least 3 times above normal values; (4) urine amylase at least 3 times above normal values; (5) findings of acute edematous pancreatitis on ultrasound or on computed tomography; and (6) absence of any primary liver disease.

Patients were considered to have SIRS as defined by the American College of Chest Physicians/Society of Critical Care Medicine (ASCP/SCCM) Consensus Conference Committee[29]. These criteria include 2 or more of the following conditions: (1) body temperature > 38C or < 36°C; (2) increased pulse rate of > 90 beats/min; (3) tachypnea, manifested by respiratory rate > 20 breaths/min, or hyperventilation, as indicated by a Pa_{CO2} of < 32 torr (4.26 kPa); and (4) alteration in WBC count of > 12 × 10^9/l or < 4 × 10^9/l, or the presence of > 10% immature neutrophils (band).

Sepsis was defined as a systemic response to infection including the criteria for SIRS plus microbiological evidence of a focal infection and/or a positive blood culture. Inclusion criteria for sepsis were the following in accord with the ASCP/SCCM 1997 classification[30]: (1) clinically proven infection with fever as its first manifestation over the last 12 h before admission, and (2) SIRS. Primary infections for sepsis were urinary tract infection and lower respiratory tract infection.

Serum lactic dehydrogenase (LDH) levels were measured by UV-kinetic method with the Olympus AU2700 autoanalyzer (Olympus Diagnostics GmbH, Hamburg, Germany). Serum albumin levels were measured by a colorimetric method with an Olympus AU2700 autoanalyzer.

The study was conducted in accord with the Helsinki Declaration. Informed consent was obtained from all patients or the next of kin if patients were unconscious. The study was approved by the ethics committee of Gülhane Military Medical Academy.

Genetic analysis. Blood samples were taken at the Department of Medical Genetics. DNA extraction was undertaken using the QIAamp® DNA Mini Kit (Qiagen No. 51306, Qiagen GmbH, Hilden, Germany) as described[31]. Patients were investigated using the Pronto™ FMF Basic Kit (Savyon Diagnostics, No. 9904, Ashdod, Israel) for the presence of 5 pyrin gene mutations (M694V, M680I, V726A, R761H, and M694I) commonly encountered in our population.

Statistical analysis. Data were analyzed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA) statistical software. Descriptive data were shown as mean ± SD. Differences in parameters between patients with and without pyrin mutations were investigated by Mann-Whitney U-test. To compare pyrin mutation ratios of the groups with frequency of carriers in a healthy Turkish population[20] we used the t test for one proportion (NCSS 2005, NCSS Inc., Kaysville, UT, USA). A value of $p = 0.05$ was evaluated as statistically significant.

RESULTS

We tested M694V, M680I, V726A, R761H, and M694I mutations in our patients. Test results for 80 patients and 160 chromosomes are shown in Table 1. Twenty-four out of 80 (30%) critically ill patients were identified to carry pyrin mutations; none had a personal or family history compatible with FMF. We found a high frequency of carriers in patients having pneumonia (30.3%), urinary tract infection (29.4%), and acute pancreatitis (30.8%). The distribution of pyrin mutations among critically ill patients was as follows: M694V 21.3%, M680I 8.7%, V726A 0%, R761H 0%, and M694I 0%.

When we compared our results with the pyrin mutation carrier rate of a previous study (10%)[11], the rates of pyrin mutations in all patients ($p < 0.001$), patients with urinary tract infec-

Table 1. MEFV genotyping in critically ill patients.

Pyrin Mutation	Patients with Pneumonia, n = 33	Patients with Urinary Tract Infection, n = 34	Patients with Acute Pancreatitis, n = 13
M694V	8	6	3
M680I	2	4	1
V726A	—	—	—
R761H	—	—	—
M694I	—	—	—
Total (%)	10 (30.3)	10 (29.4)	4 (30.8)

tion ($p < 0.001$), acute pancreatitis ($p < 0.001$), and pneumonia ($p < 0.001$) were found to be significantly high (Table 2).

The WBC count, erythrocyte sedimentation rate, LDH, and fever and pulse rate were significantly higher, whereas systolic and diastolic blood pressure and albumin levels were significantly lower in patients with pyrin mutation compared to those without this mutation (Table 3). The age, sex, body mass index, respiratory rate, hemoglobin, hematocrit, platelet count, blood glucose, creatinine, urea, lipid profile, and liver function tests did not differ significantly between patients with and those without pyrin mutation (data not shown).

DISCUSSION

To our knowledge, this study is the first attempt to investigate the rate of pyrin mutations in critically ill patients with SIRS and sepsis. We found that 30% of these patients carry at least one of the pyrin mutations. We also observed a high frequency of carriers in patients having pneumonia (30.3%), urinary tract infection (29.4%), and acute pancreatitis (30.8%). Yilmaz, *et al*[20] established the frequencies of pyrin mutations in 100 healthy individuals of a Turkish population. Their results reveal a carrier rate of 20% in the Turkish population. However, E148Q was very frequent (12%) as well among the healthy population in that study[20]. Since pyrin E148Q has been considered to be a normal variant, it was not included in our study. Therefore, we compared our carrier rate for pyrin mutations with results from Yilmaz, *et al*[20] after exclusion of pyrin E148Q mutations. This observation, along with the absence of diagnostic criteria for FMF in critically ill patients, suggests that critically ill patients with SIRS and sepsis have increased prevalence of pyrin mutations compared to the frequency of carriers in the previous report (10%)[20]. It seems likely that pyrin mutations may also be a susceptibility factor for the development of SIRS and sepsis. Our results support the hypothesis of Kalyoncu, *et al* that the carrier status for pyrin mutations seems to cause an alteration in the state of health[25]. In view of our findings, carriers for pyrin mutations appear to have a worse disease progress; it is reasonable to assume that mutations in pyrin may modify the course of the disease.

In our study, critically ill patients showed the following pyrin mutation rates: M694V 21.3%, M680I 8.7%, V726A 0%, R761H 0%, and M694I 0%. Yilmaz, *et al*[20] reported the distribution of pyrin mutations was E148Q 12%, M680I 5%, M694V 3%, V726A 2%, and M694I 0% in healthy individuals. In a recent study[32], *MEFV* genotyping in 49 healthy Turkish controls showed that 4 (8.2%) subjects carried E148Q, 2 (4.1%) were M694V, one (2%) was K695R, one (2%) was V726A, one (2%) was M694V/E148Q, and one (2%) was V726A/E148Q[33]. In another study, Imirzalioglu *et al*[31] reported that the mutation frequency in M694V was 6.1% (4/66), M680I 3% (2/66), and E148Q 1.5% (1/66) in 66 healthy subjects.

How mutations in pyrin might increase the susceptibility and severity of SIRS and sepsis is unclear, but this may be related to the function of pyrin. Pyrin is an antiinflammatory

Table 2. Rate of pyrin mutations in critically ill patients and comparison of carrier stage ratio in healthy subjects of Yilmaz, *et al* study[20].

Cause of SIRS and Sepsis	Carrier Rate for Pyrin Mutations (%)	Carrier Rate for Pyrin Mutations in Healthy Subjects*[11], %	t	p
Urinary tract infection	10/34 (29.4)	10	122.367	< 0.001
Acute pancreatitis	4/13 (30.8)	10	58.788	< 0.001
Pneumonia	10/33 (30.3)	10	119.361	< 0.001
Total	24/80 (30)	10	188.138	< 0.001

* After exclusion of E148Q.

Table 3. Comparison of clinical and laboratory variables between patients with and without pyrin mutations.

Variable	Patients with Pyrin Mutations, n = 24	Patients without Pyrin Mutations, n = 56	t	p
Body temperature, ˚C	39.79 ± 0.79	38.74 ± 0.69	5.789	< 0.001
Pulse rate, beats/min	114.50 ± 9.11	95.12 ± 8.77	8.941	< 0.001
SBP, mmHg	111.09 ± 21.85	137.37 ± 16.09	–5.973	< 0.001
DBP, mmHg	70.01 ± 11.63	85.54 ± 8.44	–6.761	< 0.001
White blood cell count, 10^9/l	18.65 ± 3.55	12.59 ± 2.89	8.443	< 0.001
ESR, mm/h	53.97 ± 14.66	30.83 ± 7.58	6.103	< 0.001
Serum albumin, g/l	33.3 ± 0.61	39.5 ± 0.73	–4.421	0.001
Lactic dehydrogenase, U/l	350.56 ± 114.67	201.08 ± 95.08	6.675	0.001

ESR: erythrocyte sedimentations rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

molecule induced by Th2 cytokines, and may be part of the homeostatic response to endotoxin and nuclear factor-κB (NF-κB) activation[34]. Conceptually, in individuals with the wild-type *MEFV* gene, pyrin plays a key role in regulating the intensity of the inflammatory response. In contrast, individuals with one or more missense mutations at the *MEFV* locus produce a pyrin protein with altered or absent function. Pyrin presumably participates in a complex interplay with the PYD protein superfamily and lipopolysaccharides via the TLR family and procaspase-1 (IL-1ß-converting enzyme) activation. It is also implicated in homeostatic control of inflammation through leukocyte apoptosis and IL-1ß and NF-κB activation[34-36]. Caspase-1, in turn, cleaves the 31-kDa precursor form of IL-1ß into its biologically active 17-kDa fragment, a potent mediator of fever and inflammation[37]. Caspase-1 is also essential for innate antibacterial host defenses and may represent a mechanism of innate immunity that upon excessive stimulation by microbial components leads to endotoxic shock[38]. Pyrin inhibits caspase-1 and IL-1ß activation[34]. Mice expressing a truncated, hypomorphic pyrin variant exhibit heightened sensitivity to endotoxin challenge, with increased activation of both caspase-1 and IL-1ß[34]. Sarkar, *et al* reported that caspase-1-knockout animals were protected from bacterial challenge, whereas wild-type IL-1ß-knockout and IL-1ß/IL-18 double-knockout animals were not[39]. On the other hand, although the precise mechanism is still under investigation, pyrin also disrupts NF-κB activation in transfected cells[40-42]. NF-κB is an important transcription factor involved in the initiation and resolution of inflammation through induction of proinflammatory gene products. Bohrer, *et al*, investigating peripheral blood monocytes of patients with sepsis, found that NF-κB activation predicts mortality[43]. Finally, since pyrin seems to modulate the activity of apoptotic proteins and signal transduction pathways, playing a crucial role in the inflammatory pathways of the innate immune system[44], exacerbated activation of the innate immune response with the consequent increase of proinflammatory cytokines due to pyrin mutations may contribute to the development of SIRS and sepsis. Therefore, it may be speculated that carrier status in FMF brings a disadvantaged condition for those people, rather than an advantage, with respect to survival.

Some limitations of our study exist. First, the presence of other currently unrecognized pyrin mutations that may have affected our results. Second, the lack of some immunological measures; and third, longterm followup studies are needed for clarification of morbidity and mortality rates in SIRS and sepsis patients having any pyrin mutation. Studies are also necessary to derive some preventive measures to protect the carriers against life-threatening conditions. Although we did not screen relatives of these critically ill patients for pyrin mutations, the family history for FMF manifestations was negative. No patient in our study had any FMF symptomatology. In this context, *MEFV* genotyping has contributed greatly to the knowledge of FMF, but the diagnosis remains predominantly clinical[45]. However, it would be interesting to know the ratio of patients with true FMF in patients critically ill with SIRS and sepsis, and also the severities of clinical features. But it has been calculated that for a general intensive care unit population with sepsis, a sample size of 2000 patients would be required to detect a relative risk for mortality of 1.5 from any polymorphism[46]. In this context, given the modest likely effect of genetic variants on risk or outcome in sepsis, it is likely that study populations exceeding 2000 patients will be needed to confidently exclude any possible associations[33]. Therefore, our report should be considered a pilot study that requires validation with replication in large consecutive studies or by pooling data for metaanalysis.

Our results showed that patients critically ill with SIRS and sepsis have increased prevalence of pyrin mutations, and patients with SIRS and sepsis carrying pyrin mutations seem to be highly susceptible for a severe disease course. Our data may provide some new insight into understanding of individual genetic differences in susceptibility to SIRS and sepsis. It appears to be important in the field of critical care to identify genetically high-risk patients by pyrin mutation analysis. However, longitudinal studies involving larger populations are needed to document the role of pyrin mutations in the risk of developing SIRS and sepsis.

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