VALIDATION OF A DIAGNOSTIC SCORE FOR THE DIAGNOSIS OF AUTOINFLAMMATORY DISEASES IN ADULTS

L. CANTARINI[1], F. IACOPONI[2], O.M. LUCHERINI[3], L. OBICI[4], M.G. BRIZI[1], R. CIMAZ[5], D. RIGANTE[6], M. BENUCCI[7], G.D. SEBASTIANI[8], A. BRUCATO[9], L. SABADINI[10], G. SIMONINI[5], T. GIANI[5], F. LAGHI PASINI[11], C.T. BALDARI[3], F. BELLISAI[1], G. VALENTINI[12], S. BOMBARDIERI[13], G. PAOLAZZI[14] and M. GALEAZZI[1]

[1]Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, University of Siena; [2]Department of Biomedical Sciences, Applied Biology Section, University of Siena; [3]Department of Evolutionary Biology, University of Siena; [4]IRCSS Fondazione Policlinico S. Matteo, Pavia; [5]Department of Paediatrics, Rheumatology Unit, Anna Meyer Children's Hospital and University of Florence; [6]Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Rome; [7]Rheumatology Unit ASL 10, Nuovo Ospedale S. Giovanni di Dio, Florence; [8]UOC of Rheumatology, S. Camillo-Forlanini Hospital, Roma; [9]Internal Medicine, Ospedali Riuniti di Bergamo, Bergamo; [10]Rheumatology Unit, Ospedale S.Donato ASL 8, Arezzo; [11]Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Immunological Sciences Unit, Policlinico Le Scotte, University of Siena; [12]Rheumatology Unit, Second University of Naples; [13]Rheumatology Unit, Department of Internal Medicine, University of Pisa; [14]Department of Rheumatology, S. Chiara Hospital, Trento, Italy

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The first two authors contributed equally to this study

Most autoinflammatory disorders typically come out in the pediatric population, although a limited number of patients may experience disease onset during adulthood. To date, a late disease onset has been described only in familial Mediterranean fever, caused by mutations in the *MEFV* gene, and in tumor necrosis factor receptor-associated periodic syndrome, caused by mutations in the *TNFRSF1A* gene. The relative rarity and lack of information on adult-onset autoinflammatory diseases make it likely that mutations will be found in an even smaller percentage of cases. With the aim of improving the genetic diagnosis in adults with suspected autoinflammatory disorders, we recently identified a set of variables related to the probability of detecting gene mutations in *MEFV* and *TNFRSF1A* and, in addition, we have also proposed a diagnostic score for identifying those patients at high risk of carrying mutations in these genes. In the present study we evaluated the preliminary score sensitivity and specificity on a wider number of patients in order to validate the goodness of fit of the model. Two hundred and nineteen consecutive patients with a clinical history of periodic fever attacks were screened for mutations in *MEFV*

Key words: autoinflammatory disorders, tumor necrosis factor receptor–associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF), diagnostic criteria

Mailing address: Luca Cantarini, MD, PhD
Rheumatology Unit,
Policlinico Le Scotte,
University of Siena,
Viale Bracci 1, 53100 Siena, Italy
Tel: ++39 347 9385457 Fax: ++39 0 577 40450
e-mail: cantariniluca@hotmail.com

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and *TNFRSF1A* genes; detailed information about family/personal history and clinical manifestations were also collected. For the validation of the score we considered data both from the 110 patients used to build the preliminary diagnostic score and from the additional 219 patients enrolled in the present study, for a total number of 329 patients. Early age at disease onset, positive family history for recurrent fever episodes, thoracic pain, abdominal pain and skin rash, which are the variables that had previously been shown to be significantly associated with a positive genetic test result (12), were used for validation. On univariate analysis the associations with a positive genetic test were: age at onset (odds ratio [OR] 0.43, p=0.003), positive family history for recurrent fever episodes (OR 5.81, p<0.001), thoracic pain (OR 3.17, p<0.001), abdominal pain (OR 3.80, p<0.001) and skin rash (OR 1.58, p=0.103). The diagnostic score was calculated using the linear combination of the estimated coefficients of the logistic multivariate model (cut-off equals to 0.24) revealing good sensitivity (0.778) and good specificity (0.718). In conclusion, our score may serve in the diagnostic evaluation of adult patients presenting with recurrent fever episodes suspected of having an autoinflammatory disorder, helping identify the few subjects among them who may be carriers of mutations in *MEFV* and *TNFRSF1A* genes.

Hereditary periodic fever syndromes (HPFSs) are a group of inherited disorders of the innate immune system caused by mutations of genes involved in the regulation or activation of the inflammatory response, which belong to the category of autoinflammatory disorders (1-3). These conditions are characterized by self-limited recurrent fever attacks in association with multi-district inflammation mainly involving skin, serosal membranes and joints (3-4). Between attacks, patients feel well and regain their normal daily functions until the next episode occurs. Most HPFSs typically manifest in the pediatric population, although a limited number of patients may experience disease onset during adulthood. To date, a late disease onset has been described only in familial Mediterranean fever (FMF) (5-6) and in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (7-8), the most common autosomal recessive and autosomal dominant HPFSs, respectively. FMF is caused by mutations in the *MEFV* gene, which encodes a protein known as pyrin (9-10), and TRAPS is caused by mutations in the *TNFRSF1A* gene, which encodes the 55-kD receptor for tumor necrosis factor (TNF)-α (11).

In FMF clinical manifestations of adults are similar to those of younger patients (5), whereas adult-onset TRAPS patients may present a phenotype mimicking FMF even in the duration of inflammatory attacks, which can be shorter than usual, frequently leading to misdiagnosis and improper management (12-13). In addition, patients with adult-onset TRAPS may present atypical clinical manifestations mimicking autoimmune disorders (13-16). With the aim of improving the genetic diagnosis in adults with suspected autoinflammatory disorders, we recently identified a set of variables related to the probability of detecting gene mutations in *MEFV* and *TNFRSF1A* and, in addition, we also proposed a diagnostic score for identifying those patients at high risk of carrying mutations in these genes (12).

In the present study we have evaluated the preliminary score sensitivity and specificity on a larger number of patients in order to validate the goodness of fit of the model.

MATERIALS AND METHODS

Patients

We enrolled 219 consecutive new patients. The majority (207/219) were Caucasians of Italian ancestry and all patients were seen at our Institutions between June 2009 and October 2010. Criteria for inclusion in the screening group were: 1) periodic fever attacks of unknown origin, with fever- and symptom-free intervals associated with normal levels of acute-phase reactants, and 2) one or more of the following symptoms present during fever attacks: abdominal pain, chest pain, lymphadenopathy (documented by imaging techniques: echotomography, magnetic resonance imaging and/or high resolution computed tomography, which were performed in order to rule out underlying disorders), splenomegaly (echotomographic evaluation), cutaneous manifestations, musculoskeletal involvement, oral aphthosis, ocular involvement (periorbital edema and/or conjunctivitis) and orchitis. Detailed information about family/personal history, and clinical manifestations were collected retrospectively.

For FMF, homozygous and compound heterozygous

patients were considered to be genetically positive, while for TRAPS, heterozygous patients were considered to be genetically positive.

The study was approved by the Ethics Board of the Azienda Ospedaliera Universitaria Senese, Siena, Italy. Each patient had previously provided written consent for genetic testing, in accordance with the Helsinki Declaration and local Ethics Committee regulations, and also provided written consent for inclusion in the study.

DNA extraction

Mononuclear cells were purified from peripheral blood of healthy donors and patients by density gradient centrifugation on Ficoll-Paque (Amersham Biosciences, Buckinghamshire, UK). Genomic DNA was isolated from peripheral blood lymphocytes of patients and healthy controls using QIAamp DNA mini Kit (Qiagen, Hilden Germany).

Genomic DNA amplification and mutation detection

The *MEFV* gene exons 2, 3, 5 and 10, where the majority of known mutations are found, and *TNFRSF1A* gene exons 2, 3, 4 and 6, which encode the extracellular domain of the 55 kD receptor for TNF-α (17), were amplified by polymerase chain reaction (PCR), using Expand High Fidelity PCR System (Roche, Germany). PCR products were purified using the Wizard SV Gel and PCR Clean-Up System (Promega, Madison, WI, USA). Sequencing was carried out (Bio-Fab Research srl, Italy) on the ABI 3730 DNA analyzer (Applied Biosystems) using the same primers as those used for PCR.

Statistical methods

For validation of the diagnostic score, we included in the statistical analysis data both from the 110 patients used to build the preliminary diagnostic score (6) and from the additional 219 patients enrolled in the present study, for a total number of 329 patients. Early age at disease onset, positive family history for recurrent fever episodes, thoracic pain, abdominal pain and skin involvement, which are the variables that had previously been shown to be significantly associated with a positive genetic test result (12), were used for validation of the score. The variables that were not significantly associated with a positive genetic test in the preliminary score (musculoskeletal involvement, ocular involvement, periorbital edema, headache, lymphadenopathy, duration of fever, oral aphthosis and splenomegaly) were not considered as possible risk factors and were not included in the statistical analysis. The associations among the variables chosen for score validation and presence or absence of at least one of the mutations as an outcome was evaluated by *chi*-square test.

Univariate logistic regression analysis was performed to identify the variables, which were significantly associated with positive genetic test results. A multivariate logistic model was created through stepwise forward-backward analysis with a probability for entry equal to 0.05 and for removal equal to 0.10 and a classification cut-off equal to 0.50, including the constant in the model, if significant. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each risk factor as exponential of variable coefficients (beta). The significant betas (significance evaluated by Wald test) of these variables were used as additive components in the linear combination to construct the score.

The ROC Curve (Receiver Operating Characteristic) procedure provided a useful way to evaluate the performance of classification schemes that categorize cases into one of two groups (positive or negative). Only symptoms that were correlated at a 5% significance level with a specific disease category in the univariate analysis by *chi*-square test or Fisher's exact test were included as continuous variables in the regression tree analysis.

A p value <0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed using the software package SPSS version 16.0 (SPSS, Inc. Chicago, IL).

RESULTS

At the time of genetic testing, the majority of the patients (187/219; 85.39%) were over the age of 16. The mean age of enrolled patients was 34.48 years (range 0.5–66 years) and the mean age at disease onset was 23.67 years (range 0.3–59.0 years).

Of the 219 patients enrolled in this study, 173 did not have mutations in the examined regions of the 2 genes, whereas 46 patients, all Caucasians, were identified as having homozygous or compound heterozygous mutations in *MEFV* (18 patients) or heterozygous mutations in *TNFRSF1A* (28 patients). Table I summarizes the frequencies of the clinical manifestations in patients with both positive and negative genetic tests, and Table II shows patients' genetic characteristics. Data are reported as absolute frequencies and percentages (%).

Results of univariate and multivariate logistic analysis are shown in Table III. Most variables (abdominal pain, thoracic pain, age at onset, positive family history) were associated with the outcome by an OR significantly different from 1. Only skin rash was shown to be not significant, with a p value of 0.103.

Table I. *Clinical characteristics of genetically positive and genetically negative patients.*

Independent variable	***TNFRSF1A*** (n=28)	***MEFV*** (n=18)	**No mutations** (n=173)
Abdominal pain	11 (39.29%)	14 (77.78%)	32 (18.50%)
Thoracic pain	16 (57.14%)	12 (66.67%)	66 (38.15%)
Skin rash	10 (35.71%)	10 (55.56%)	67 (38.73%)
Musculoskeletal involvement	15 (39.29%)	15 (83.33%)	109 (63.01%)
Ocular involvement	6 (21.43%)	3 (16.67%)	24 (13.87%)
Perorbital edema	2 (7.14%)	2 (11.11%)	27 (15.61%)
Headache	7 (25.00%)	6 (33.33%)	24 (13.87%)
Lymphadenopathy	7 (25.00%)	6 (33.33%)	47 (27.17%)
Age at onset (>16 yrs)	13 (46.43%)	8 (44.44%)	144 (83.24%)
Positive family history	14 (50.00%)	4 (22.22%)	11 (6.36%)
Duration of fever (> 7 days)	14 (50.00%)	0 (0%)	54 (31.21%)
Oral aphthosis	3 (10.71%)	2 (11.11%)	41 (23.70%)
Splenomegaly	--	1 (5.55%)	24 (13.87%)
Orchitis	--	--	--

Table II. *Genetic characteristics of patients with a positive genetic test.*

TRAPS			
	Low penetrance	**High penetrance**	**Others**
	R92Q *(15)*	T50M *(2)*	e.586-612del27 *(1)*
	V95M *(2)*	C43Y *(1)*	c.394-399del *(1)*
	P46L *(2)*	C52Y *(1)*	
		C43R *(1)*	
		C88Y *(1)*	
		S59P *(1)*	
FMF			
	Homozygous	**Compound Heterozygous**	
	E148Q *(2)*	R202Q + K695R *(3)*	
	K695R *(2)*	E148Q + A744S *(2)*	
	M694V + R202Q *(2)*	M694V + R408Q *(1)*	
	E148Q + R202Q *(1)*	E148Q + R408Q+R202Q *(1)*	
		P639S + R408Q+ R202Q *(1)*	
		E148Q + A744S+ R202Q *(1)*	
		E148Q + R408Q *(1)*	
		P639S + R408Q *(1)*	

List of abbreviations: TRAPS, tumor necrosis factor receptor-associated periodic syndrome; FMF, familial Mediterranean fever; pts, patients. In parenthesis the number of patients for each mutation.

In the multivariate model the variables abdominal pain, thoracic pain and skin rash were re-coded according to frequency (never, sometimes, often, always), age at disease onset was re-coded into classes of age in decades (<10, 11-20, 21-30, 31-40, 41-50, 51-60, >60) and positive family history was considered as a dichotomous variable (presence/absence), as shown in Table IV. The results of

Table III. *Estimations derived from univariate and multivariate logistic regression analysis.*

Independent variable	Univariate analysis		Multivariate analysis				
	OR (95% CI)	*p* value	beta	S.E.	Wald	OR (95% CI)	*p* value
Abdominal pain	3.80 (2.15-6.72)	<0.001	0.51	0.14	13.40	1.67(1.27-2.20)	<0.001
Thoracic pain	3.17 (0.77-5.65)	<0.001	0.69	0.14	24.16	1.99(1.51-2.61)	<0.001
Skin rash	1.58 (0.91-2.75)	0.103	0.28	0.15	3.59	1.32(0.99-1.77)	0.058
Age at onset (>16 yrs)	0.43 (0.25-0.76)	0.003	-0.97	0.38	6.68	0.38(0.18-0.79)	0.01
Positive family history	5.81 (3.17-0.65)	<0.001	0.55	0.20	7.63	1.73(1.17-2.54)	0.006

Table IV. *Variables included in the final model for the calculation of the diagnostic score.*

Variable	Coding	Beta	Diagnostic Score
Age at onset	Age class*	-0.97	- 0.97 x age class*
Abdominal pain	Never=0 Sometimes=1 Often =2 Always=3	0.51	Never=0 Sometimes = 0.51 Often = 1.02 Always = 1.53
Thoracic pain	Never=0 Sometimes=1 Often =2 Always=3	0.69	Never = 0 Sometimes = 0.69 Often = 1.38 Always = 2.07
Skin rash	Never=0 Sometimes=1 Often =2 Always=3	0.28	Never=0 Sometimes= 0.28 Often = 0.56 Always= 0.84
Positive family history	Negative=0 Positive =1	0.55	Negative=0 Positive = 0.55

** Age classes (pt): 7, <10 yrs; 6, 11-20 yrs; 5, 21-30 yrs; 4, 31-40 yrs; 3, 41-50 yrs; 2, 51-60 yrs; 1, >60 yrs*

multivariate analysis showed the skin rash at the limit of significance (OR=1.324, p=0.058), while all other variables preserved their significance as risk factors or as factors having a protective role (12). In fact, higher age at disease onset appeared to be a protective factor with regard to the presence of mutations (OR=0.378, p=0.01). In the final model, we introduced the intercept (- 2.543) that was statistically significant in the multivariate model, thus obtaining the final score: | SCORE | = - 2.543 + $0.514\ X_1 + 0.686\ X_2 + 0.281\ X_3 - 0.973\ X_4 + 0.545\ X_5$ where | SCORE | is the score expressed as absolute value (modulus), X_1 abdominal pain, X_2 thoracic pain, X_3 skin rash, X_4 age at onset, X_5 positive family history. It will be 3.516 when a patient is over 60 years of age, has a negative family history for periodic or recurrent fever episodes and presents no symptoms other than fever. It will be 4.366 when a patient is under 10 years of age, has a positive family history for recurrent fever episodes and has all the highest-frequency symptoms. A score greater than 14% (> 3.635 points) will identify patients at high risk of carrying mutations in the genes under consideration, whereas a lower percentage score (<

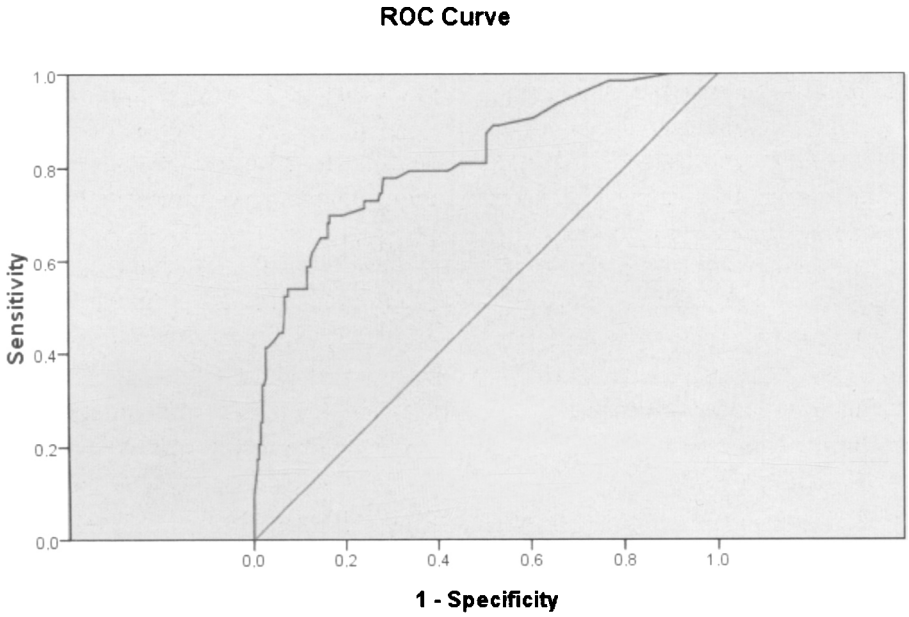

Fig. 1. *ROC curve for the 329 patients included in the validation model, indicating a sensitivity of 0.778 and a specificity of 0.718.*

3.635 points) will indicate a low risk.

The score cut-off value (14%) was determined as the optimal level of sensitivity and specificity, and then standardized as a percentage. To obtain a standardized score in percentage, it is necessary to adjust the minimum score of 3.516 to 0 and the maximum score of 4.366 to 0.85 and calculate the percentage by proportions.

The constructed additive model to calculate the score gave a significant (p<0.001) area under curve (ROC analysis) which equals to 0.815 (CI 95% 0.755-0.878) and assessed the performance of the model (Fig. 1). By correspondence of a cut-off of 0.14, we obtained the sensitivity of 0.778 – meaning that approximately 77.8% of all positive test patients would be correctly identified as such - and the specificity of 0.718 (1-specificity = 0.282), meaning that 28.2% of all negative test patients would be incorrectly identified as positive.

As previously described (12), univariate analysis confirmed that although fever attacks lasted less than 1 week in about half of the patients with mutations in the *TNFRSF1A* gene, this variable showed a significantly different incidence between the two genes (p=0.021).

DISCUSSION

The HPFSs currently include two autosomal recessive conditions - FMF (*Mendelian Inheritance in Man*, MIM 249100) and hyper-immunoglobulinemia D (HIDS, MIM 260920) - and a group of autosomal dominant diseases, including TRAPS (MIM 142680) and cryopyrin-associated periodic syndromes (CAPS) (4). Most HPFSs typically have onset in the pediatric age, ranging from the first hours to the first decade of life, while a limited number of patients experience disease onset during adulthood. Onset of HIDS typically occurs in the first year of life, and genetic testing is unnecessary in patients who have their first fever attack when they are over the age of 5 (18). CAPS are also characterized by early disease-onset and, in addition, their chronic disease course and their well-distinguished clinical features may help establishing a differential diagnosis (19-20). For these reasons, since our study involved mainly adults, only FMF and TRAPS were considered.

To date, the rate of detecting autoinflammatory gene mutations in patients suspected of having an autoinflammatory disorder is very low (21-23).

However, most data refer to pediatric populations (22-23). With the aim of improving diagnosis of HPFs by increasing the probability of obtaining positive results for genetic testing in children under the age of 10, a diagnostic score was recently proposed (24). When testing our adult-disease-onset patients characterized using this pediatric score, most subjects carrying mutations were identified as low-risk patients. This was probably related to the fact that, since the score is valid for children, advanced age of disease onset had a highly protective role. In addition, most patients carrying low-penetrance *TNFRSF1A* variants were characterized by incomplete disease and atypical clinical manifestations. We recently proposed a preliminary score for the evaluation of adults with suspected autoinflammatory disorders, based on data from 110 patients (12). In the present study we have validated the same score on a larger number of patients. Two hundred and nineteen additional patients were enrolled and the statistical analysis also included data from the 110 patients in the previous study, for a total of 329 patients. Since the majority of patients were of Italian origin, multivariate analysis could not evaluate the ethnic origin of patients among the possible discriminating variables. Nevertheless, ethnic origin should obviously be taken into account when considering patients from populations with a high prevalence of mutations of a certain gene (21). The same is true in the case of patients who meet diagnostic criteria for FMF (25).

Different from the preliminary score, where the skin rash was shown to be definitely significant with an OR of 1.845 ($p<0.003$), this variable lost its significance in this validation study ($p=0.058$). Nonetheless, we decided to include the contribution of skin rash in the final model, since lack of statistical significance does not necessarily imply lack of clinical relevance, and also because lack of statistical significance in the validation study - unlike in the preliminary study - may have depended on the sample of newly-enrolled patients.

Significance was however confirmed for all of the other originally-considered risk factors. Advanced age at disease onset preserved its value as a protective factor and all the other variables (abdominal pain, thoracic pain and positive family history for periodic fever attacks) were confirmed as risk factors, contributing to the probability that a given patient would be a carrier of a mutation in the two genes under consideration.

Multivariate regression underlined the simultaneous effect of the implied variables on the probability of mutation. The constructed score considers this simultaneous effect of independent variables, combining each variable with a weight proportional to the probability of mutation. The predictive potential of the model is demonstrated by the high levels of sensitivity (77.8%) and specificity (71.8%) obtained by ROC analysis, which underlines the high level of predictiveness of the score. The cut-off obtained through a combination of predicted probability of sensitivity and specificity is equal to the optimal cut-off previously estimated (12).

In conclusion, our score may serve in the diagnostic evaluation of adult patients presenting with recurrent fever episodes suspected of having an autoinflammatory disorder, helping identify the few subjects who may be carriers of mutations in the *MEFV* and *TNFRSF1A* genes. Nevertheless, further evaluation by longitudinal studies on different ethnicities and different populations deriving from other geographical areas is necessary to definitively verify both sensitivity and specificity of the proposed score.

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