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Curriculum Reumatologia Pediatrica

The Eurofever Registry of Autoinflammatory Diseases: 10 years of enrollment

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Alla mia famiglia

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Chapter 1 – INTRODUCTION:

1.1 The Autoinflammatory Diseases

The autoinflammatory diseases (AIDs) are a group of inflammatory conditions related to abnormal regulation of innate immunity[1], caused by mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. The first gene identified was the MEFV gene in 1997.The spectrum of autoinflammatory disorders ranges from monogenic diseases such as FMF to multifactorial diseases like Behcet syndrome.[2] Over the last decade, a number of monogenic and multifactorial diseases have been identified or reclassified as autoinflammatory in aetiology[3]. Due to their genetic nature, most of these disorders have an early onset, ranging from the first hours to the second decade of life. Only a limited number of patients experience a disease onset during adulthood[4]. Clinically the autoinflammatory syndromes are characterized by recurrent flares of systemic inflammation presenting in the majority of cases as sudden fever episodes associated with elevation of acute phase reactants together with a number of clinical manifestations such as rash, serositis (peritonitis, pleurisy), lymphadenopathy and arthritis. Symptom-free intervals are characterized by complete wellbeing, normal growth and complete normalization of acute phase reactants. Familial Mediterranean fever (FMF, MIM 249100), mevalonate-kinase deficiency (MKD, MIM 260920) and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS, MIM 142680) are the three monogenic disorders subsumed under the term periodic fevers. A systemic inflammation dominated by a characteristic urticarial rash associated with a number of other clinical symptoms is typical of familial cold autoinflammatory syndrome (FCAS, MIM 120100), Muckle-Wells syndrome

(MWS, MIM 191900) and chronic infantile neurological cutaneous and articular syndrome (CINCA, MIM 607115). These diseases represent the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome 1 (CIAS-1, or NLRP3) coding for a protein called cryopyrin. Hence these disorders are also known under the term cryopyrin-associated periodic syndromes (CAPS). Other conditions are characterized by the appearance of typical granulomatous formations (granulomatous disorders). Blau's syndrome (MIM 186580), also known as familial juvenile systemic granulomatosis, presents with noncaseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis and uveitis) and is associated with mutations of the NACHT domain of the gene CARD15 (or NOD2). Of note is that mutations in this same gene have been associated with Crohn's disease, another granulomatous disease. Other rare disorders dominated by the presence of sterile pyogen abscesses chiefly affecting skin, joints and bones (pyogenic disorders) include the PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne) (MIM 604416), associated with mutations of the CD2-binding protein 1 (CD2BP1 or PSTPIP1) gene, the Majeed syndrome (MIM 609628), characterized by chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia and neutrophilic dermatosis, caused by mutations of LPIN2 gene, and deficiency of the interleukin-1receptor antagonist (DIRA) (MIM 612852), a recently identified autosomal recessive autoinflammatory syndrome characterized by severe systemic inflammation beginning approximately at the time of birth with multifocal osteomyelitis, periostitis and pustulosis and caused by mutations of the IL1RN gene encoding interleukin-1 receptor antagonist. Even if nowadays there is much more awareness of these

disorders, the extreme rarity and relatively recent identification as autonomous entities, often result in delayed diagnosis.

Clinical Presentation	Disease	Gene	Main clinical features
Periodic Fever	Familial Mediterranean Fever	MEFV	Short duration of fever episodes: 24–48 hours. Abdominal and chest pain. Erysipelas-like erythema. Renal amyloidosis in untreated patients. Good response to colchicine. Possible response to IL-1 blockade
	Mevalonate Kinase deficiency	MVK	Early onset Mean duration of fever episodes: 4–5 days. Poor conditions during fever episodes. Abdominal pain, vomiting and diarrhea. Splenomegaly. Good response to steroids. High rate of self-resolution during adulthood.
	TNF-receptor associated periodic syndrome	TNFRSFS1A	Prolonged fever episodes: 1–3 weeks. Periorbital edema, monocytic fasciitis. Incidence of renal amyloidosis: 15–25%. Response to TNF- and IL-1 blockade.
Sistemic inflammation and urticarial rash	Familiar Cold autoinfiammatory Sindrome Muckle-Wells syndrome Chronic infantil neurological cutaneous and articular syndrome	NLRP3	FCAS: rash, fever and arthralgia after cold exposure. MWS: recurrent or sub-chronic urticaria-like lesions, sensorineural hearing loss, amyloidosis. CINCA: mental retardation, chronic aseptic meningitis and bone deformities. Good

			response to IL-1 blockade.
	FCAS2	NLRP12	Periodic fever after cold exposure, hearing loss.
	NLRC4-associated disease	NLRC4	Urticarial rash, enterocolitis, recurrent MAS
Granulomatosis diseases	Blau's syndrome	CARD15	Early onset. Polyarticular granulomatous arthritis, uveitis, skin rash. Good response to anti-TNF monoclonal antibodies.
Bone- Joint-Skin inflammation	PAPA syndrome	PSTPIP1	Pyogenic sterile arthritis, pyogenic gangrenosum, cystic acne. Good response to IL-1 blockade
	COPA	COPalfa	Early polyarthritis, lung involvement
	Majeed syndrome	LPIN2	Multifocal osteomyelitis, congenital dyserythropoietic anaemia, inflammatory dermatosis
	DIRA	IL1RN	Neonatal-onset multifocal osteomyelitis, periostitis, and pustulosis. Dramatic response to anakinra
	DITRA	IL36RN	Generalized pustular psoriasis, recurrent fever
	CAMPS	CARD14	Generalized pustular psoriasis
Polyarteritis Nodosa and Early Stroke	ADA2 Adenosine deaminase deficiency	CERC1	Recurrent fever, livedo reticularis, stroke, hypogamaglobulinemia, vasculopathy PAN-like
Panniculitis/ lipodystrophy	CANDLE	PSMB8, PSMA3, PSMB4, PSMB10	Early onset. Fever, arthritis, dactylitis, panniculitis, progressive lipodystrophy and articular contracture, mental delay.

	ORAS	FAM105B	Neonatal onset of fever, diarrhea, panniculitis
Vasculopathy and ulcers	SAVI	TMEM173	Early vasculopathy with interstitial lung involvement
	A20 halpoinsuficiency	TNFAIP3	Behcet like sympotms
Bowel inflammatory disease	Early onset IBD	IL10, IL10RA, IL10RB	Early onset IBD (<2 years)
Autoinflamation with Imunodeficiency	HOIL-1 deficiency	RBCK1, HOIL-1	Recurrent systemic inflammation, hepato-splenomegaly, lymphadenopathy impaired response anti-virus and bacteria
	PLAID/APLAID	PLCgamma2	Skin lesions, cellulitis, interstitial lung disease, athralgia, uveitis, bowel inflammatory disease, variable deficit of B cells
Multifactorial diseases	CNO	-	Recurrent steril osteomyelitis
	Behcet syndrome	-	Recurrent oral-genital ulcers
	PFAPA syndrome	-	Periodic fever, aphthous stomatitis, adenitis

Table 1: Classification of Autoinflammatory Diseases (from Federici et al, 2012)

Chapter 2 - AIM OF THE STUDY:

The aim of the present study is to perform a descriptive evaluation of demographic features (geographic distribution, diagnostic delay, genetic analysis), clinical manifestation, response to treatment and safety of AIDs using data extrapolated from the International Eurofever Registry. Further aim is to focus on genetic analysis, with particular interest about pathogenic/non

pathogenic variants and to analyze the most used therapeutic strategy in different countries, with particular attention for biologic drugs. Finally, after ten years from its creation, to examine Eurofever impact on Scientific community.

Chapter 3 – METHODS:

The data analyzed in the study were extracted from the Eurofever registry, which is hosted in the PRINTO website. From February 2015 we started the longitudinal collection of follow-up data for the patients already included in the Registry with particular focus on treatment, modification of the clinical picture, onset of complication/adverse events. We have included in the present study all the patients enrolled in the registry with complete demographic data up to 28 September 2018.

3.1 The creation of Eurofever Registry

In 2008, thanks to a grant from the European Agency for Health and Consumers, an international initiative related to the novel group of rare conditions included under the umbrella term of autoinflammatory diseases was started: the Eurofever project. One of the main goal of the project was to establish an international registry on these rare conditions. At variance with the previous international initiatives which aimed to collect data of patients affected only by a single condition (MKD registry, Eurotraps, PFAFA registry), the Eurofever registry was conceived as a single source of information for known and future autoinflammatory diseases. Indeed, the major advantage of a single registry for different conditions is related to the possibility to collect demographic, genetic and clinical information in a homogenous fashion facilitating the comparison among the various conditions. Thanks to

collaboration with the Paediatric Rheumatology International Trials Organization (PRINTO, http://www. printo.it), the Eurofever registry was able to reach a large number of pediatric rheumatology centers already involved in the management of pediatric rheumatic conditions. Moreover, adult centers and members of the International Society of Systemic Autoinflammatory Diseases (ISSAID) and the European League Against Rheumatism (EULAR) were also engaged in the project in order to collect data also on adult patients. Indeed, the Eurofever project survey involved all centers linked to PRINTO that currently includes more than 400 centers in 60 countries worldwide. Beside the registry, the Eurofever project was an opportunity to bring together centers that care for patients with autoinflammatory diseases, establishing a network able to foster research in the field, including the organization of clinical trials. In this line, the development of new classification criteria and of new outcome measures for the autoinflammatory diseases were among the main aims of the project. The registry has elected an International Steering Committee that coordinate the all the activities of the registry.

3.2 How the Eurofever registry was developed

The registry was created in 2008 with the active collaboration of experts involved in the management of autoinflammatory diseases.[5] The experts were asked to identify all significant variables for each disorder. The forms for data collection were divided into two parts: demographic and clinical data. Demographic data included: subject ID (patients were identified by alphanumeric code), date of birth, sex, ethnicity, country of birth, onset age, date of first visit to the center, patient diagnosis and molecular analysis. Genetic testing was not mandatory, but if performed, details were requested. These

included the gene screened and whether the complete gene was sequenced or the most relevant exons or just the most relevant point mutations and the laboratory where the test was performed. Finally, information on consanguinity and any relevant family history was collected. Clinical data included: (i) signs and symptoms, (ii) laboratory examinations, (iii) imaging and other diagnostic procedures and (iv) response to treatment(s). Further revisions of the forms were subsequently evaluated by the experts and inclusion criteria for each disease were established with a final approval of the definitive version during a Consensus Meeting in March 2009. Continuous revisions of the form are performed to include newly described diseases with genetic information and associated clinical manifestations. Access to the database is available only for centers authorized by PRINTO, with a username and password on an https platform. For each disease one coordinator (Disease-PI) was chosen among the associated and collaborating partner on the basis of their expertise in the specific diseases or participation to other ongoing initiatives in connection with the Eurofever Project. Data on the single diseases are under the direct responsibility of the Disease-PIs and Eurofever's Steering Committee. Disease-PI elaborates data coming from the Registry according to the aims for their specific disease and in agreement with the Eurofever Steering Committee. General epidemiological data coming from the Registry are under the responsibility of the Steering Committee. All participants to Eurofever can prose further studies on a specific diseases or on particular aspects involving different diseases. Criteria for the evaluation of a secondary studies are the following: i) scientific relevance; ii) clinical/scientific experience of the proposer in the field; iii) number of patients enrolled in the Eurofever registry for a given disease. Ethical committee approval for patient enrollment in the registry was obtained by

participating centers as required by local legal requirements.[6] Informed consent was signed by parents or legal representatives or by the patient of adequate age. Enrollment started in November 2009. In its first version, Eurofever was established as a cross-sectional registry, collecting information of the patients from disease onset to disease diagnosis. Despite the high amount of clinical variables included, the registry was built to avoid the possibility of missing data, through the elaboration of web-based forms that do not allow the progression of data entry in case of missing data in the required field. Despite this careful approach, the main limitation of the first version of the registry was the retrospective collection of data, prompting to a possible inaccurate collection of all the clinical information pertinent to each patient. For this reason, in 2015, the registry was transformed into a longitudinal registry, collecting information on a yearly basis on the clinical evolution and the efficacy and safety of different treatments used in these rare conditions. In particular, the sections related to treatment that in the original cross-sectional version of the registry were rather concise, were completely revised in order to enable entry of more detailed information on efficacy and safety of all treatments used to treat the different autoinflammatory conditions. The creation of this large cohort of patients affected by autoinflammatory diseases with an extended follow-up will be the base for better knowledge of these disorders, with a focus on genotype/phenotype correlation and long-term efficacy and safety of different treatments. Moreover, since approximately 75–80% of patients with clinical features consistent with autoinflammatory diseases have no recognized mutations in any of the known genes,[7, 8] a large cohort of patients with undefined periodic fevers will allow characterization of novel genes in this current challenging disease group.

3.3 The Eurofever Registry objectives

1. General objectives

The main objective of Eurofever is to create a permanent network for the study of AIDs. Particularly, the project purposes are:

- To improve early diagnosis of autoinflammatory diseases;
- To give adequate information to the family of patients affected
- To improve knowledge about clinical presentation, response to treatment and complications of these rare diseases.

2. Primary Endpoints of the Registry:

1. To collect data about clinical presentation, response to treatment.
2. To evaluate moderate/severe adverse events (SAE) or events of special interest (ESI).
3. To evaluate clinical remission with or without therapy, defined as the absence of signs and symptoms, and to evaluate the improvement with AIDAI score (activity index of autoinflammatory diseases).

3. Secondary Endpoints:

1) To publish new classification criteria evidence based
2) To promote guidelines for genetic analysis
3) To create permanent network for future study
4) To identify cluster of patients of informative families with the aim to detect new genes o epigenetic factors involved in these diseases.
5) To evaluate:
   - Incidence of severe adverse events among patients treated with different drugs.

- Treatment adherence and reasons of interruption/change of therapy
- Time of relapse during treatment or after drug stop.
- Disease predictors.

3.4 Sections of the Registry

The last version of the Registry presents three main sections.

Section 1. Demographic information, diagnosis, molecular analysis

- ✓ Demographic data of the patients (sex, onset age, diagnosis age)
- ✓ Type of disease and diagnosis data
- ✓ Molecular analysis (analyzed gene, detected mutations)

Section 2. Clinical Features

- ✓ Pattern of frequency
- ✓ Number episodes/year
- ✓ Signs and symptoms related to the disease
- ✓ Routine and specific blood examinations
- ✓ Imaging and other diagnostic procedures

Section 3. Longitudinal section of the study

- ✓ Therapy and response to treatment
- ✓ Adverse events (SAE=Serious adverse events and ESI=Event of special interest)

Chapter 4 - RESULTS

4.1 General Demographic Information

In the present study we have enrolled patients included in the registry with complete demographic data up to 28 September 2018: 3843 patients (1903 M e 1940 F) with complete demographic information have been enrolled from 62 countries (geographic distribution represented in Figure 1 and Table 2).

Figure 1: Geographic distribution of patients enrolled in the study

Disease	Pts Number	Male	Female	Western-Europe (15 countries)	Eastern Europe (15 countries)	Eastern-Southern Mediterranean (8 countries)	South America	Others (Canada Messico Australia Asia)
Behcet	214	108	106	190	4	9	2	9
Blau	49	25	24	24	1	0	6	18
CAPS	298	146	152	240	13	7	9	29
CRMO	581	216	365	516	12	16	4	33
DIRA	3	0	3	2	0	1	0	0
FMF	1086	565	521	649	8	263	22	144
MKD	205	93	112	177	12	1	6	9
NALP12	13	6	7	12	0	0	1	0
PAPA	42	21	21	31	6	2	2	1
PFAPA	676	383	293	356	207	92	13	8
TNF	273	138	135	242	12	3	3	13
CANDLE	1	0	1	1	0	0	0	0
Schnitzler	13	6	7	13	0	0	0	0
Majeed	4	3	1	3	0	0	0	1
Undefined	368	182	186	301	38	9	5	15
DADA2	14	10	4	11	0	3	0	0
SAVI	3	1	2	2	0	0	1	0
Total	3843	1903	1940	2770	313	406	74	280
				72%	8%	11%	2%	7%

Table 2: Geographic distribution of patients enrolled in the study

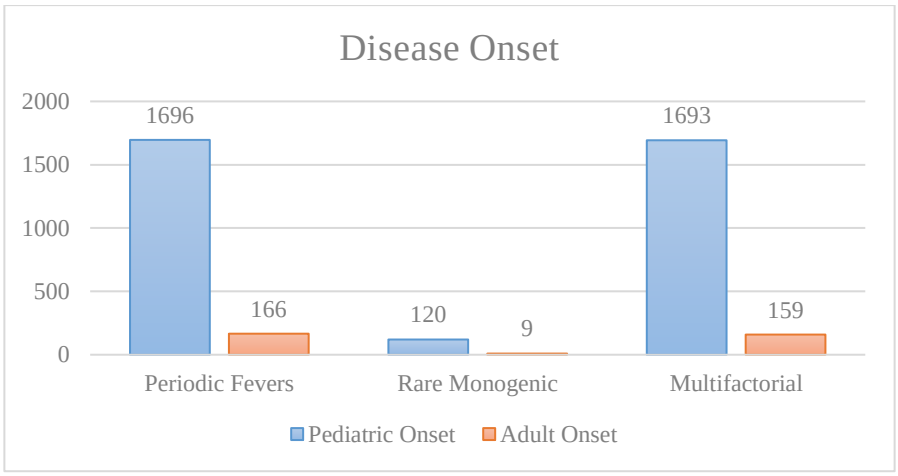
2770 (72%) are resident in Western Europe, 313 (8%) in Eastern Europe, 406 (11%) in Eastern-Southern Mediterranean (Algeria, Egypt, Israel, Lebanon, Libya, Morocco, Tunisia, Turkey), 74 (2%) in South America and 280 (7%) in other countries (35 Canada, 2 Mexico, 11 Australia, 232 Asia).

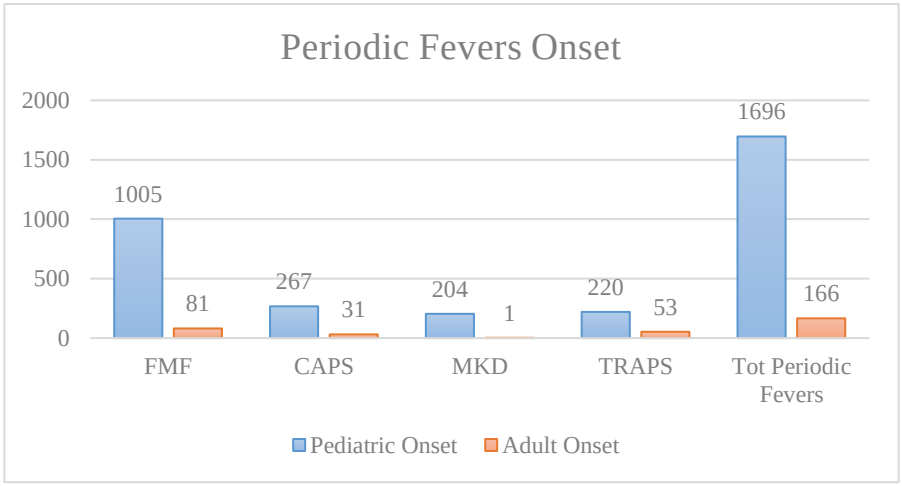
Compared to the first Eurofever report (Toplak et al, 2012[5]) we have observed an increase of enrolled patients number from East-Europe countries (from 6% to 8%), and also from Asian countries (from 3% to 6%).

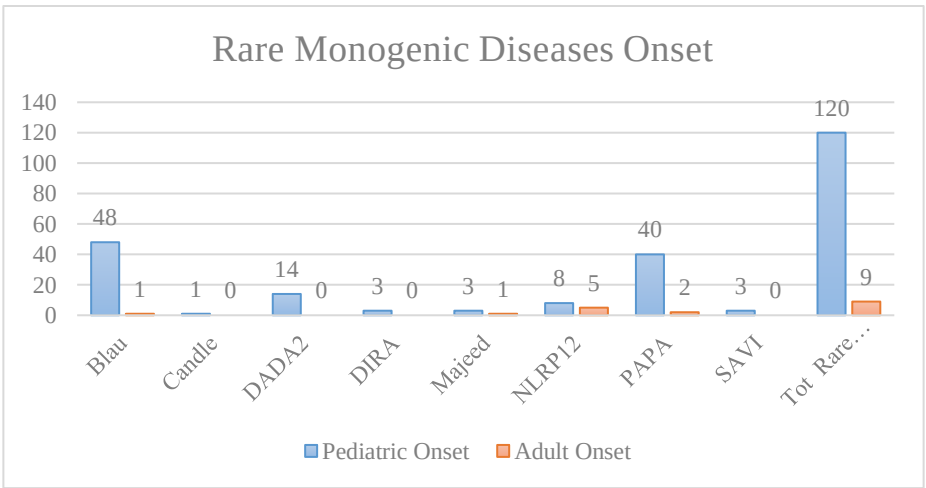
The patients enrolled are affected by the following diseases: 1862 patients affected by periodic fevers (1086 with Familial Mediterranean Fever, 298 with criopirinopathies, 205 with mevalonate kinase deficiency and 273 with tumor necrosis factor receptor associated periodic syndrome. 1852 patients are affected by multifactorial autoinflammatory diseases: 676 with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA), 581 with chronic non-bacterial osteomyelitis, 214 with Behcet disease, 13 with Schnitzler disease and 368 with unknown fever. 129 patients with rare monogenic disease: 49 Blau disease, 42 PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, acne), 14 Deficiency of adenosine deaminase 2 (DADA2), 13 associated periodic fever (NALP12), 4 Majeed, 3 deficiency of interleukin-1 receptor antagonist (DIRA), 3 STING-associated vasculopathy with onset in infancy (SAVI), 1 chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE).

4.2 Onset, Diagnosis and Enrollment

The median onset age is 4 years (range 1 month – 75 years), the median diagnosis age is 8 years (range 1 month – 78 years). 3509 (91%) patients presented disease onset during pediatric age (<16 years), 334 (9%) during adult age (81 FMF, 31 CAPS, 53 TRAPS, 40 CRMO, 12 Schnitzler syndrome e 90 unknown fever). (Figure 2) 405 of 3509 (12%) patients with pediatric onset received diagnosis during adult age (Figure 3).


Disease Onset
2000
1500
1000
500
0
1696
166
120
9
1693
159
Periodic Fevers
Rare Monogenic
Multifactorial
Pediatric Onset
Adult Onset


Periodic Fevers Onset
2000
1500
1000
500
0
1005
81
267
31
204
1
220
53
1696
166
FMF
CAPS
MKD
TRAPS
Tot Periodic Fevers
Pediatric Onset
Adult Onset


Rare Monogenic Diseases Onset
140
120
100
80
60
40
20
0
48
1
1
0
14
0
3
0
3
1
8
5
40
2
3
0
120
9
Blau
Candle
DADA2
DIRA
Majeed
NLRP12
PAPA
SAVI
Tot Rare…
Pediatric Onset
Adult Onset

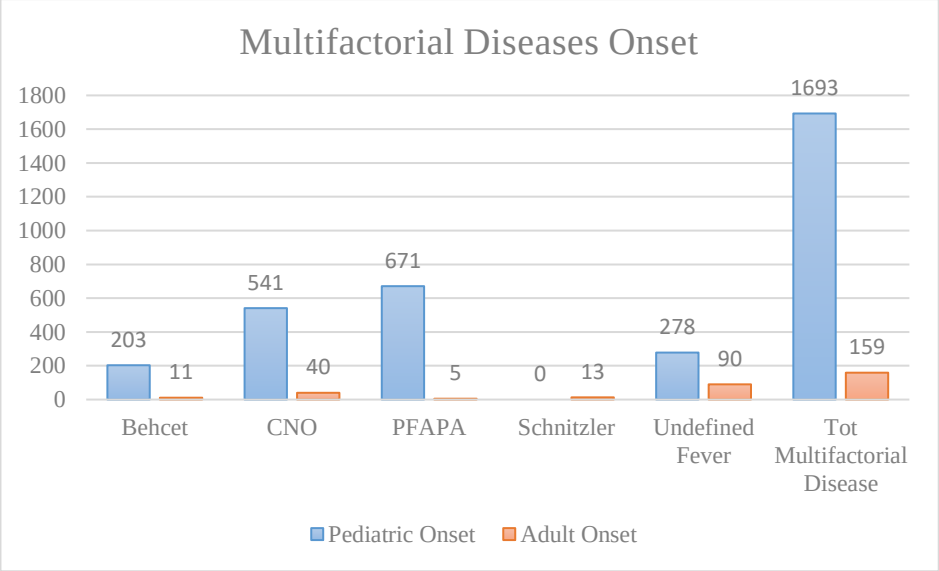


Figure 2: Pediatric/Adult onset

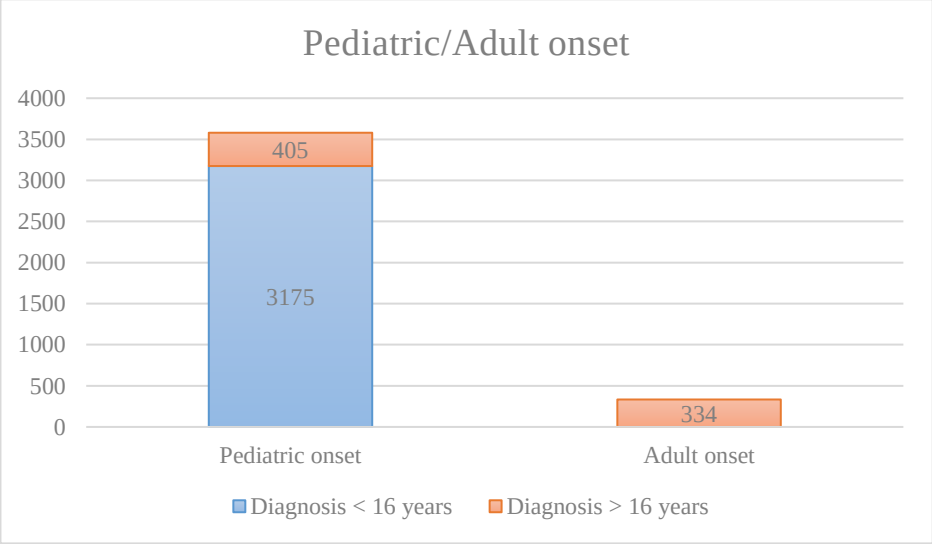


Figure 3: Pediatric/Adult onset and diagnosis

Regarding diagnostic delay (defined as time from onset and diagnosis), the median value is 5 years; diseases with longer diagnostic delay are: NLRP12 (24 years, range 4-76), CAPS (15 years, range 0-77), PAPA (14 years, range 2-57), TRAPS (12 years, range 0-77). By comparing the mean diagnostic delay from 1980 to 2018 we have observed a constant reduction of period between AIDs onset e diagnosis (Figure 4 and Table 4).

Disease	**Pts Number**	**Mean Diagnosis Delay**	**Mean Onset Age (years, range)**	**Mean Diagnosis Age**
Behcet	214	4	9 (0-56)	13 (2-57)
Blau	49	5	4 (0-30)	9 (0-46)
CAPS	298	15	5 (0-57)	20 (0-77)
CRMO	581	2	11 (0-62)	13 (1-68)
DIRA	3	2	2 mth (0-4 mth)	3 (0-7)
FMF	1086	5	6 (0-66)	11 (0-72)
MKD	205	10	2 (0-45)	12 (0-51)
NALP12	13	24	12 (0-29)	36 (4-76)
PAPA	42	14	6 (0-18)	20 (2-57)
PFAPA	676	2	3 (0-30)	5 (0-37)
TNF	273	12	10 (0-63)	22 (0-77)
CANDLE	1	9	1	10
Schnitzler	13	3	53 (36-76)	56 (41-78)
Majeed	4	5	15 (0-55)	20 (1-68)
Undefined	368	5	12 (0-73)	17 (0-75)
DADA2	14	8	4 (0-10)	12 (6-18)
SAVI	3	9	1 (0-4)	10 (1-18)
Total	3843			

Table 3: Diagnostic delay

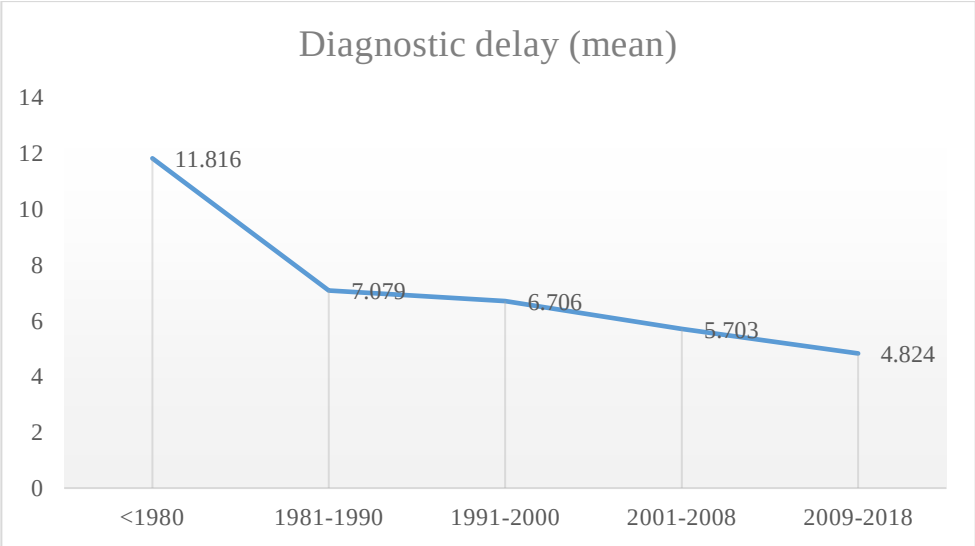


Figure 4: Diagnostic delay (mean) from 1980 to 2018

Years	Number of patients	Onset age (avarage)	Diagnosis Age (avarage)	Diagnosis delay (avarage)
<1980	6	2,235	14,051	11,816
1981-1990	19	2,318	9,397	7,079
1991-2000	170	4,517	11,223	6,706
2001-2008	1401	5,884	11,586	5,703
2009-2018	2243	8,031	12,855	4,824

Table 4: Diagnostic delay (mean) from 1980 to 2018

For 3356 (87%) patients also clinical data from onset to diagnosis, collected during the first visit performed at referred Pediatric Rheumatologic Center, are available. Since February 2015, longitudinal visits have been inserted for 477 (12%) patients, with detailed data on treatment and safety.

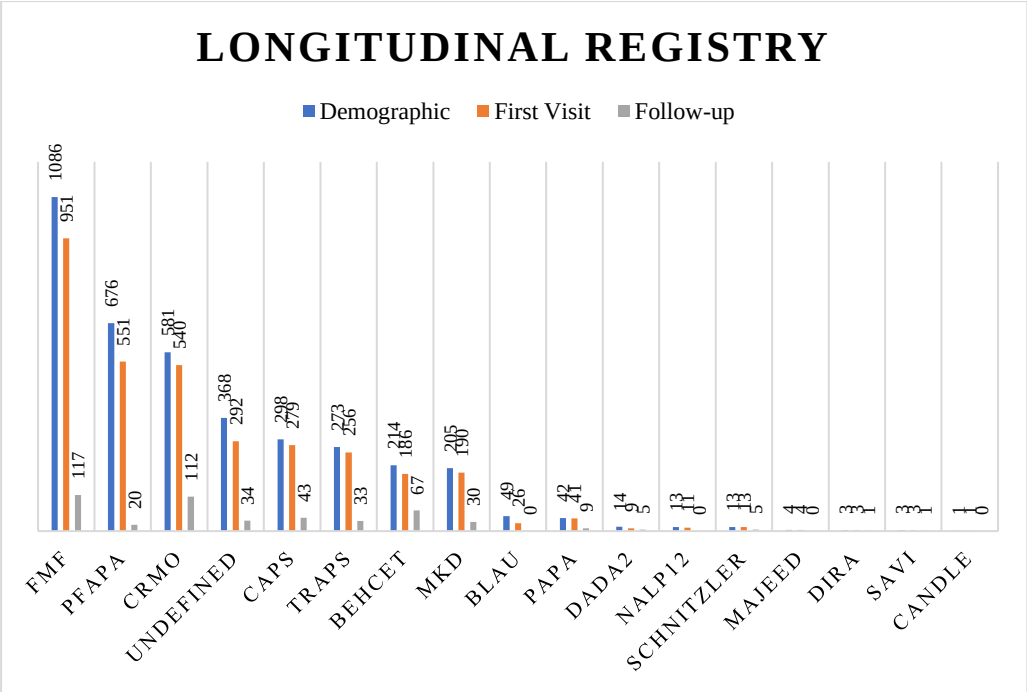
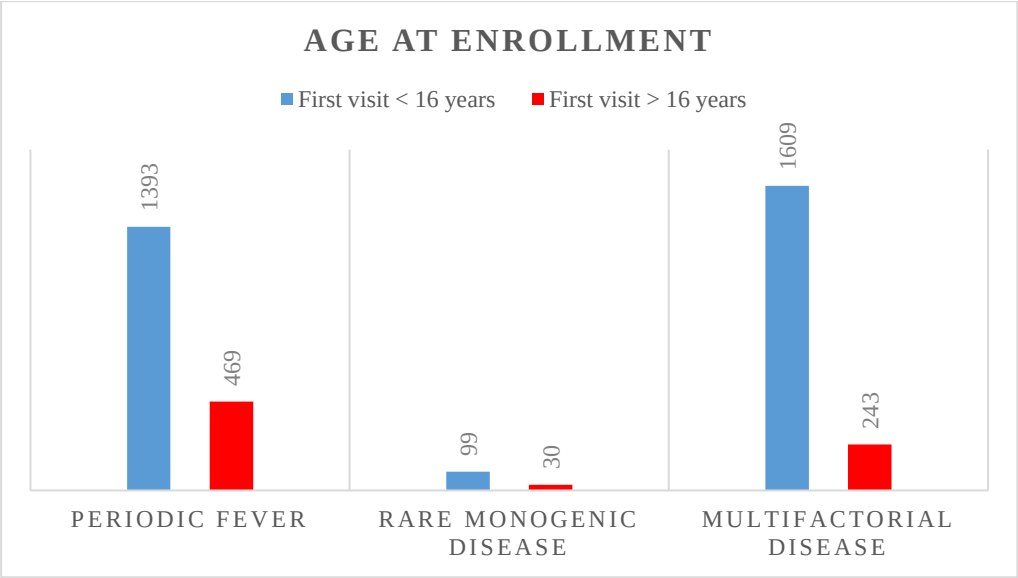
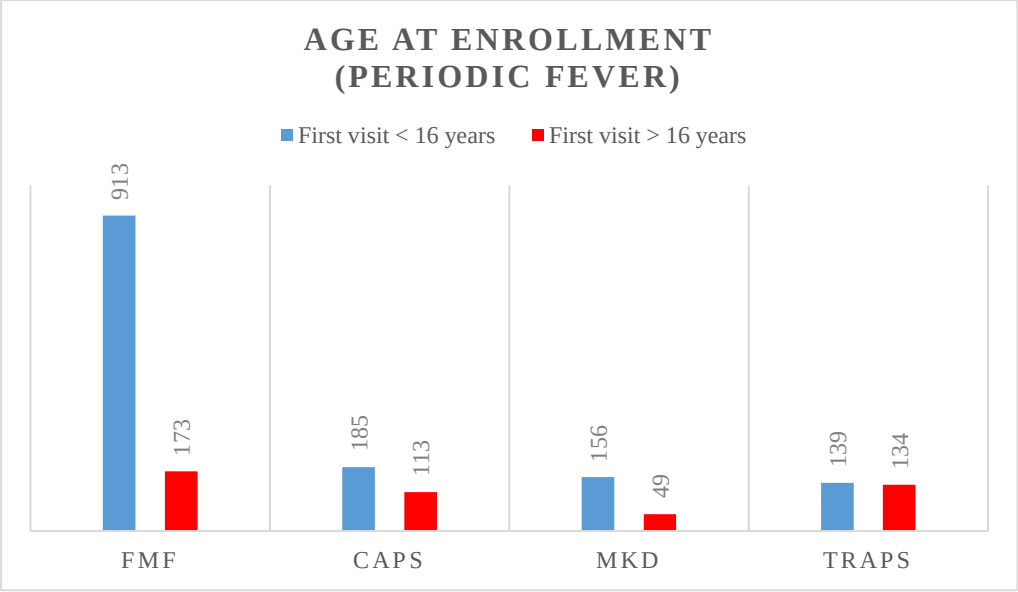


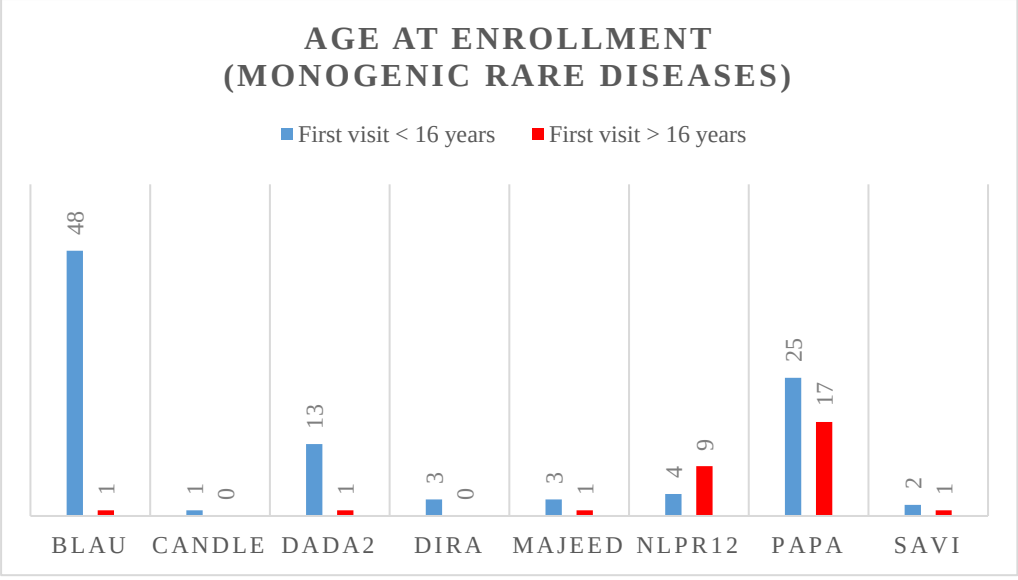
Figure 5: Number of patients enrolled in the Eurofever Registry

Regarding periodic fevers, clinical details from onset are available for l'88% (951 of 1086) of FMF patients, 94% (279 of 298) of CAPS, 76% (190 of 205) of MKD and 94 % (256 of 273) of TRAPS; complete clinical data at baseline are available for 76% (98 of 129) patients affected by Rare Monogenic Diseases and for 85% of Multifactorial Diseases (1582 of 1852).

At enrollment time, 3101 patients were in pediatric age, 742 in adult age (Figure 6).


AGE AT ENROLLMENT
First visit < 16 years
First visit > 16 years
1393
469
99
30
1609
243
PERIODIC FEVER
RARE MONOGENIC DISEASE
MULTIFACTORIAL DISEASE


AGE AT ENROLLMENT (PERIODIC FEVER)
First visit < 16 years
First visit > 16 years
913
173
185
113
156
49
139
134
FMF
CAPS
MKD
TRAPS


AGE AT ENROLLMENT (MONOGENIC RARE DISEASES)
First visit < 16 years
First visit > 16 years
48
1
1
0
13
1
3
0
3
1
4
9
25
17
2
1
BLAU
CANDLE
DADA2
DIRA
MAJEED
NLPR12
PAPA
SAVI

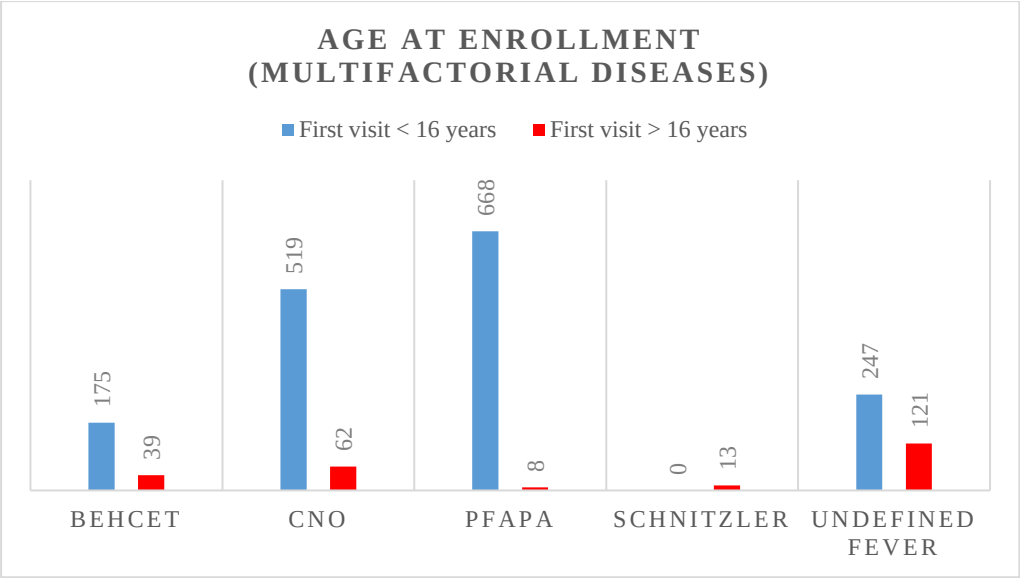


Figure 6: Age at enrollment time in AIDs

4.3 Clinical features of Periodic Fevers and PFAPA

Clinical patterns of periodic fevers are divided into:

- Continuous
- Recurrent
- Continuous-recurrent

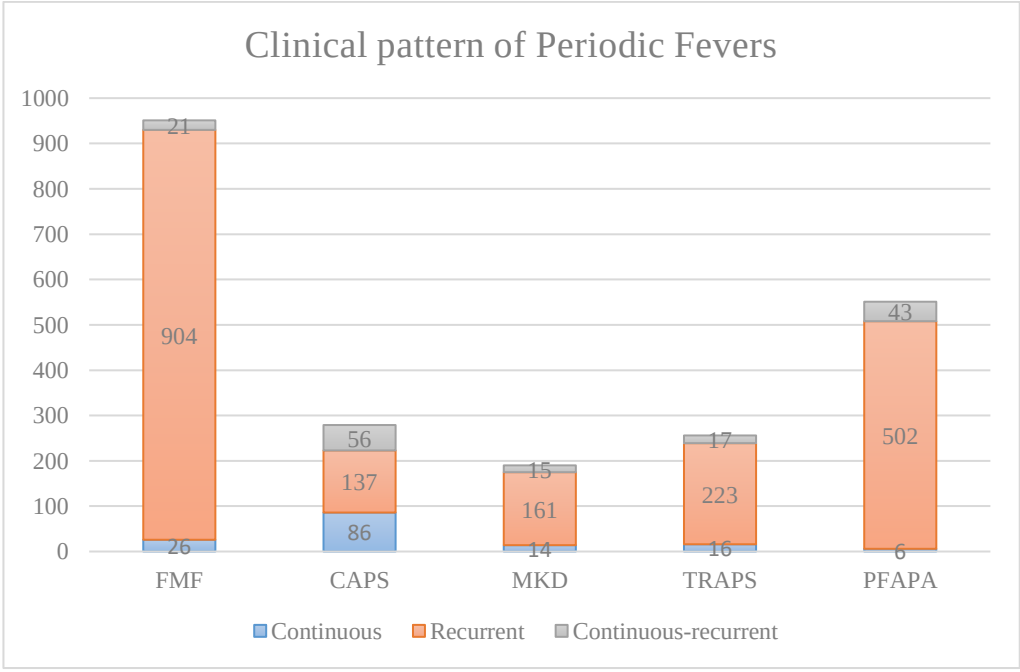


Figure 7: Pattern of presentation of Periodic Fevers

As shown in Figure 7, most of the patients are affected by recurrent diseases: 95% of patients with FMF, 49% of CAPS, l'85% of MKD, l'87% of TRAPS and 91% of PFAPA.

3% of FMF, 31% of CAPS, 4% of MKD, 6% of TRAPS and 1% of PFAPA presents continuous course. A continuous-recurrent form is observed in 2% of FMF patients, 20% of CAPS, 8% of MKD, 7% of TRAPS and 8% of PFAPA.

In order to complete the analysis of clinical features of periodic fevers the following data have been collected:

- Fever episodes duration (Figure 8)
- Number episodes/year (Figure 9)
- Pattern of frequency (regular or irregular) (Figure 10)
- Triggers (Figure 11-13): specific triggers have been found respectively in 43% of CAPS patients and 44% of MKD patients. Triggers more frequently involved are cold, stress and infections.

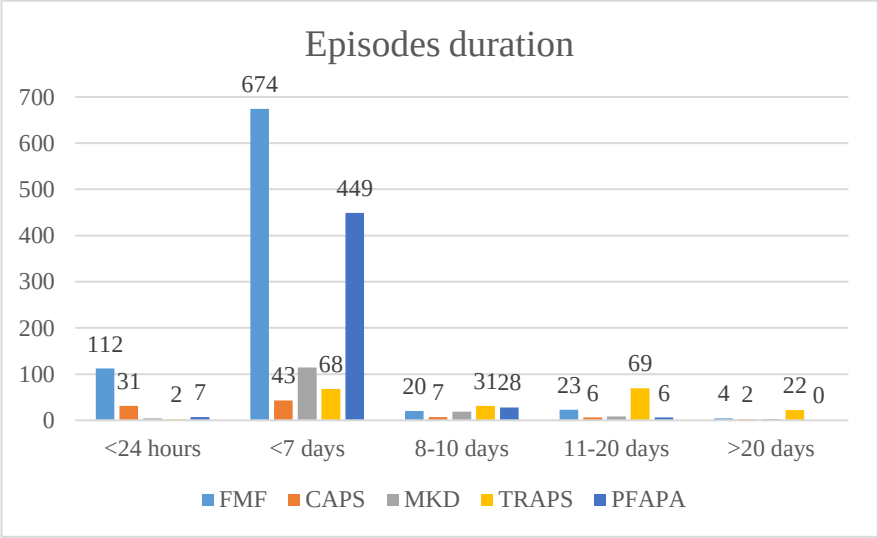


Figure 8: Fever episodes duration (number of patients)

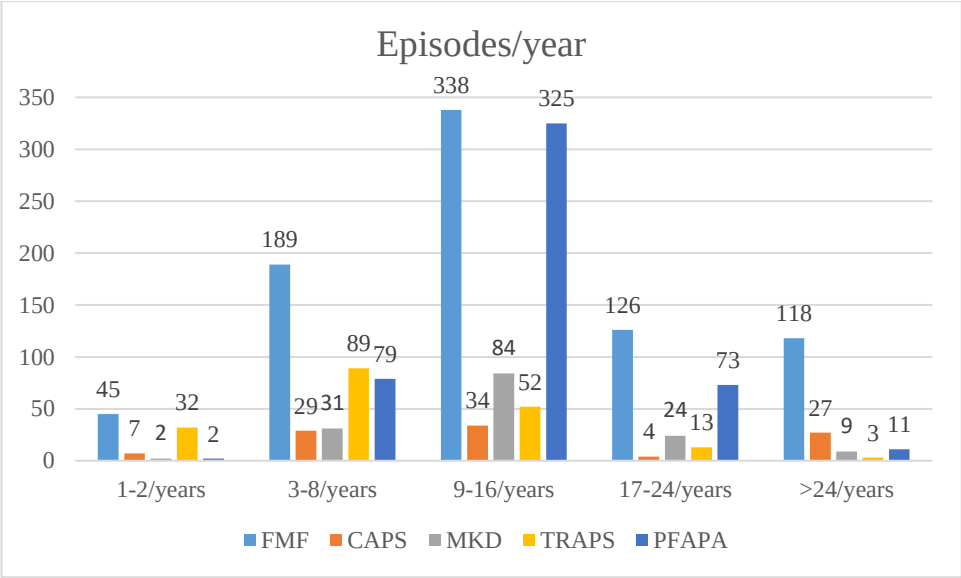


Figure 9: Number of episodes/year

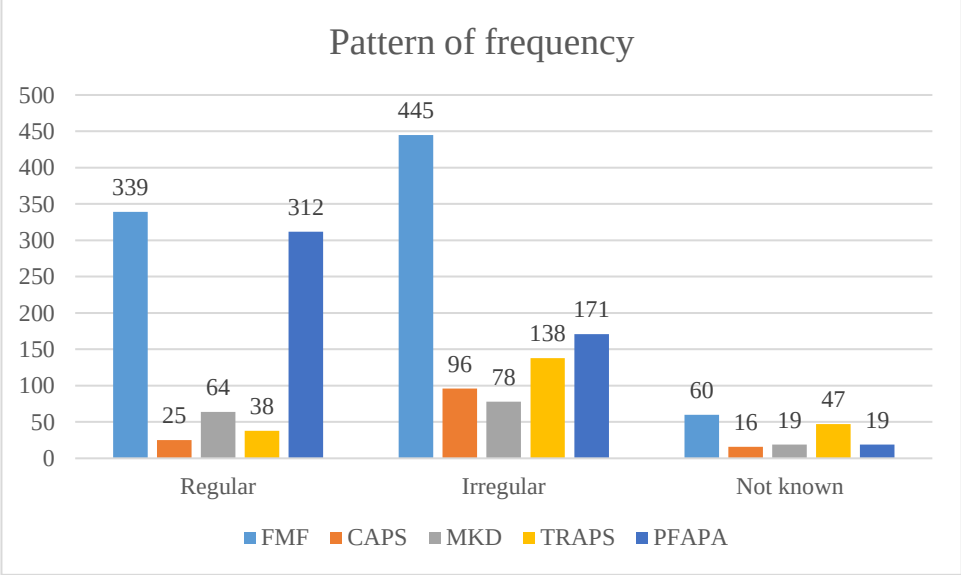


Figure 10: Pattern of frequency (regular/irregular)

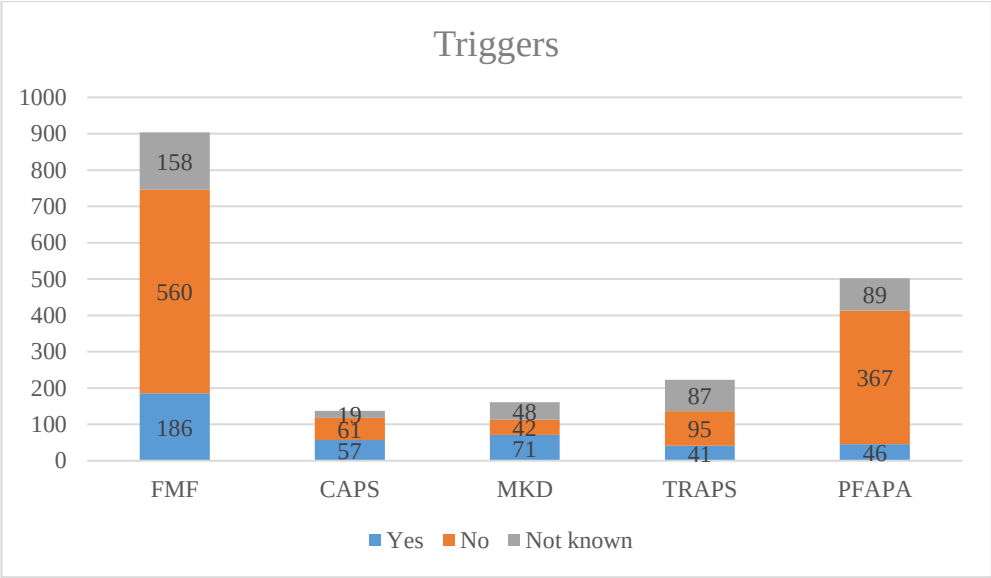


Figure 11: Triggers of episodes

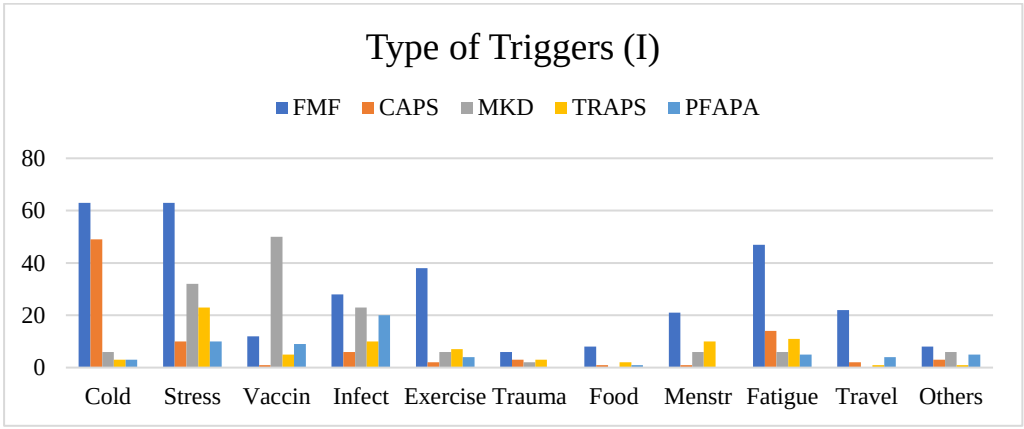


Figure 12: Type of triggers for different diseases (I)

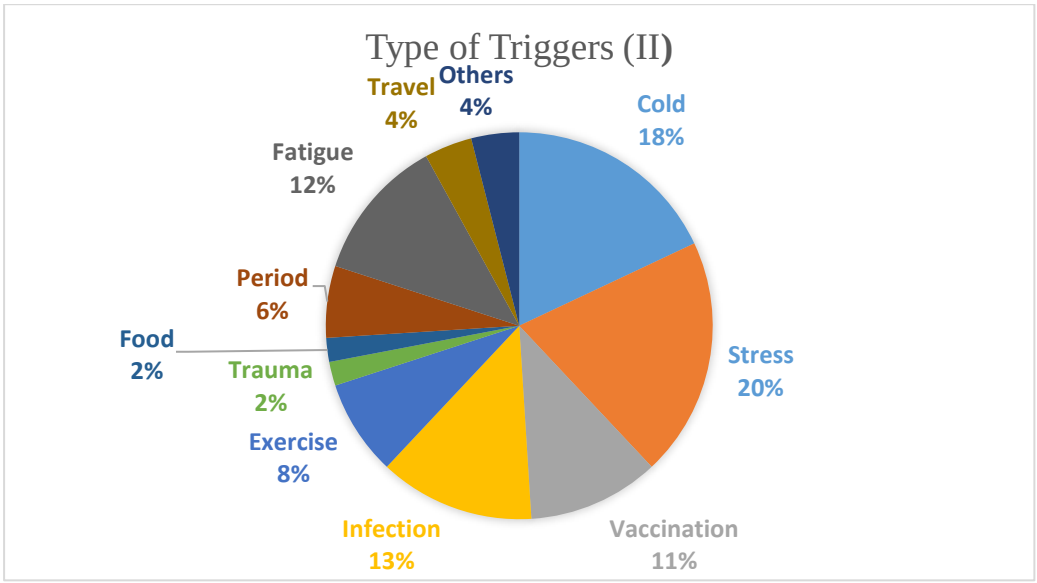


Figure 13: Type of triggers (II)

4.4 Genetic analysis

In the Registry we have identified a total of 1955 patients carriers of specific mutations: 1008 FMF, 271 TRAPS, 255 CAPS, 199 MVK, 71 Undefined Fever, 39 PFAPA, 35 PAPA, 29 Blau, 15 NALP12, 13 DADA2, 5 Behcet, 1 CANDLE, 1 DIRA, 1 Schnitzer. With the help of the Infever registry (http://fmf.igh.cnrs.fr/ISSAID/infevers, a website dedicated to mutations responsible for hereditary autoinflammatory diseases, created in 2002) we have verified the number of validates mutations and their pathogenic meaning. For MEFV gene 71% of mutations detected in patients enrolled in the Eurofever registry have been validated. 89% of mutations for NLRP3, 90% for MVK and 90% for TNFRSF1A.

Disease	Gene	N of patients	N of mutations	N validate mutations	% of validate mutations
FMF	MEFV	947	34	24	71%
FMF	TNFRSF1A	7	4	2	
FMF	MVK	4	1	1	
FMF	NLRP3	1	1	0	
CAPS	MEFV	8	1	1	
CAPS	MVK	1	1	1	
CAPS	NLRP3	207	36	32	89%
CAPS	NLRP12	1	1	1	
CAPS	TNFRSF1A	4	1	1	
MVK	MEFV	12	5	4	
MVK	MVK	171	31	28	90%
MVK	NLRP3	2	2	2	
MVK	TNFRSF1A	3	1	1	
TRAPS	MEFV	6	3	3	
TRAPS	NLRP3	2	2	1	
TRAPS	TNFRSF1A	225	40	36	90%

Table 5: Number of validated mutations for each gene of Periodic Fevers

26% of validated mutations of MEFV gene (Table 6) results pathogenic, 30% likely pathogenic; 30% of validated mutations of NLRP3 gene results pathogenic and 48% likely pathogenic; 53% of validated mutations of MVK gene results pathogenic and 33% likely pathogenic. 50% of validated mutations of gene TNFRSF1A results pathogenic, 28% likely pathogenic.

Gene	Validate mutations	Pathogenic	Likely pathogenic	Benign	Likely benign	Uncertain Significance
MEFV	27	7	8	2	3	7
NLRP3	33	11	16	1	0	5
MVK	30	16	10	2	1	1
TNFRSF1A	40	20	11	0	4	5

Table 6: Significance of validated mutations of Periodic Fevers gene

Number of patients carriers of single mutations of different AIDs are shown in Figure 14-18. In the Registry we have identified 993 patients carriers of MEFV gene mutations: 362 of them present only one mutation: in 224 patients this mutation is validated in Infever registry with pathogenic or likely pathogenic significance, while in 28 patients the mutation is benign (23 mutations R202Q, 2 D510D, 1 D102D, 1 G304R and 1 G219G). Instead, 631 patients are carriers of two mutations and 423 of them have both mutations with certain or likely pathogenic significance, 6 patients have two benign mutations (R202Q) and 16 patients have one pathogenic and one benign mutations.

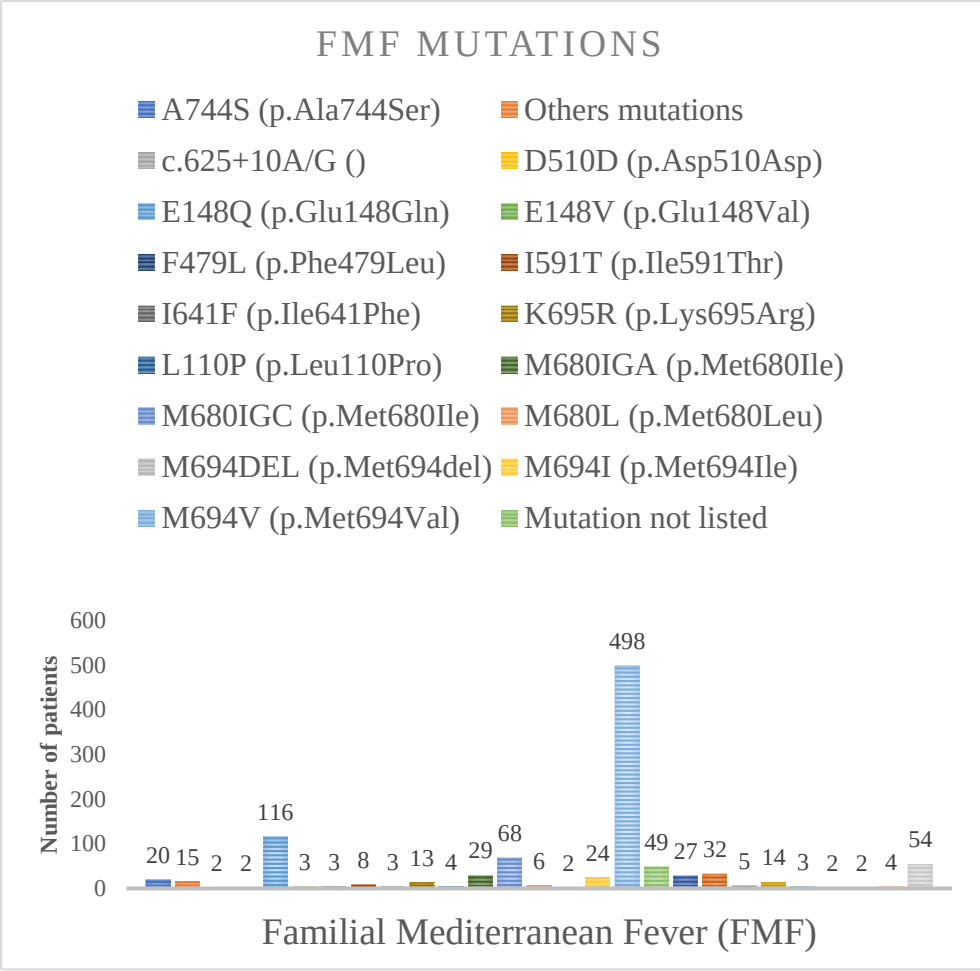


Figure 14: Number of patients carriers of MEFV gene mutations

Disease	Gene involved	Number of Patients	Number of Total Mutations	Number of Validated Mutations	Number of pathogenic/likely pathogenic Mutations	Number of Benign/likely benign Mutations
FMF	MEFV	993	38	26	15	5
FMF	TNFRSF1A	7	4	2	0	0
FMF	MVK	4	1	1	0	1
FMF	NLRP3	1	1	1	0	0

Table 7: Number of patients carriers of MEFV gene mutations

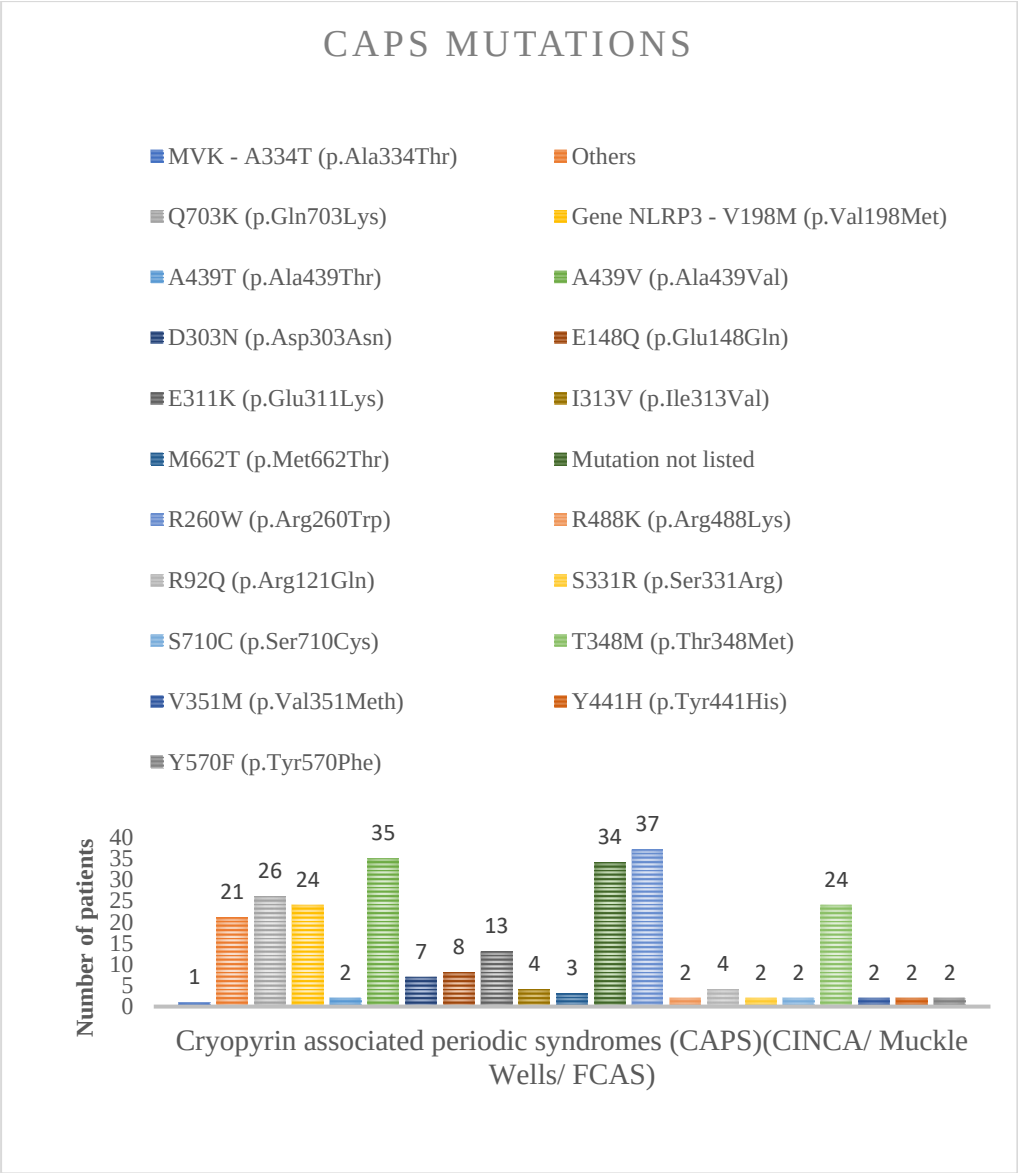


Figure 15: Number of patients carriers of NLRP3 gene mutations

Disease	Gene involved	Number of Patients	Number of Total Mutations	Number of Validated Mutations	Number of pathogenic/likely pathogenic Mutations	Number of Benign/likely benign Mutations
CAPS	NLRP3	207	36	32	28	0
CAPS	NLRP12	1	1	0	0	0
CAPS	TNFRSF1A	4	1	1	0	1
CAPS	MEFV	8	1	1	0	0
CAPS	MVK	1	1	1	1	0

Table 8: Number of patients carriers of NLRP3 gene mutations

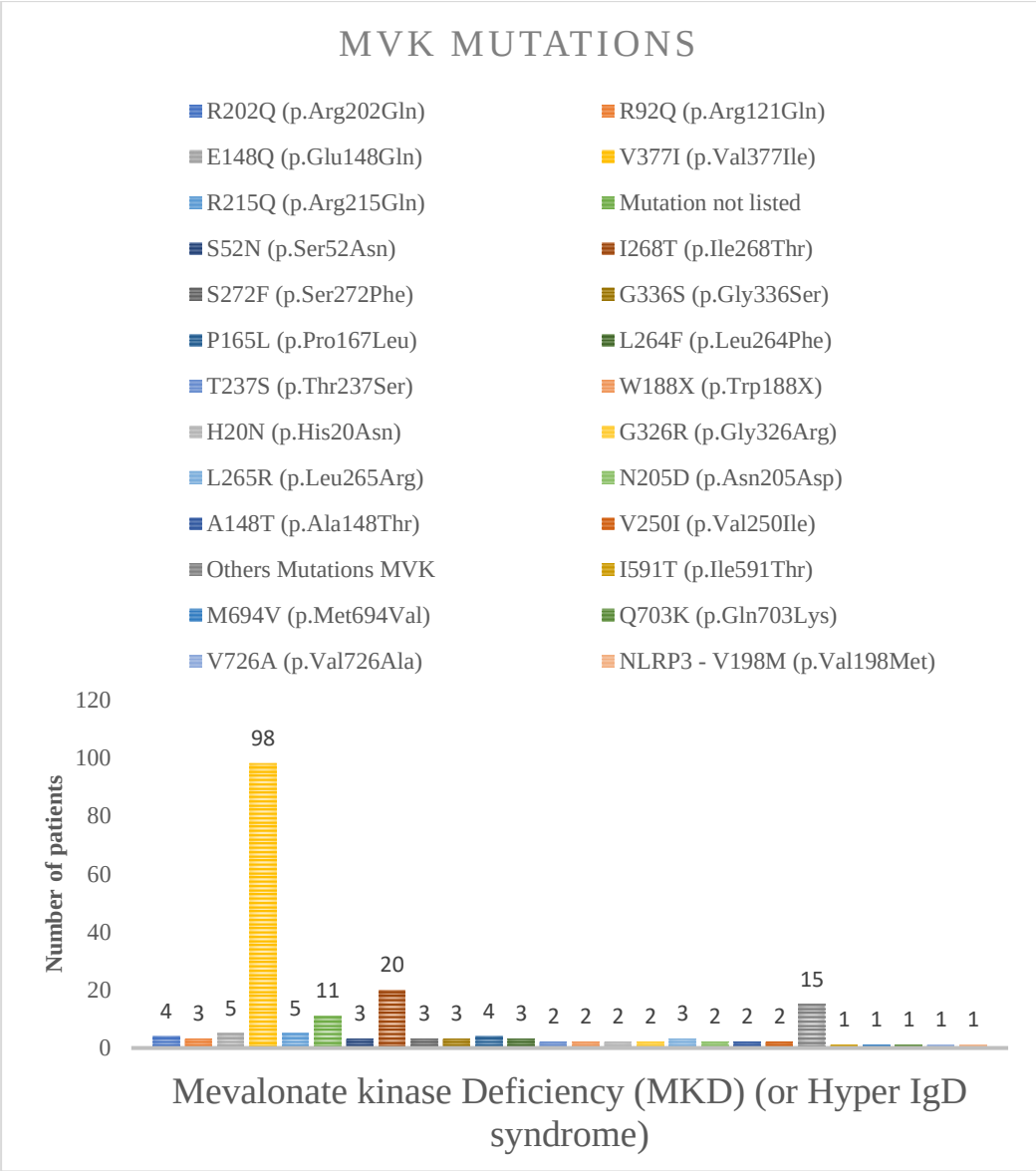


Figure 16: Number of patients carriers of MVK gene mutations

Disease	Gene involved	Number of Patients	Number of Total Mutations	Number of Validated Mutations	Number of pathogenic/likely pathogenic Mutations	Number of Benign/likely benign Mutations
MVK	MVK	171	31	28	26	2
MVK	NLRP3	2	2	2	0	0
MVK	TNFRSF1A	3	1	1	0	0
MVK	MEFV	12	5	4	2	1

Table 9: Number of patients carriers of MVK gene mutations

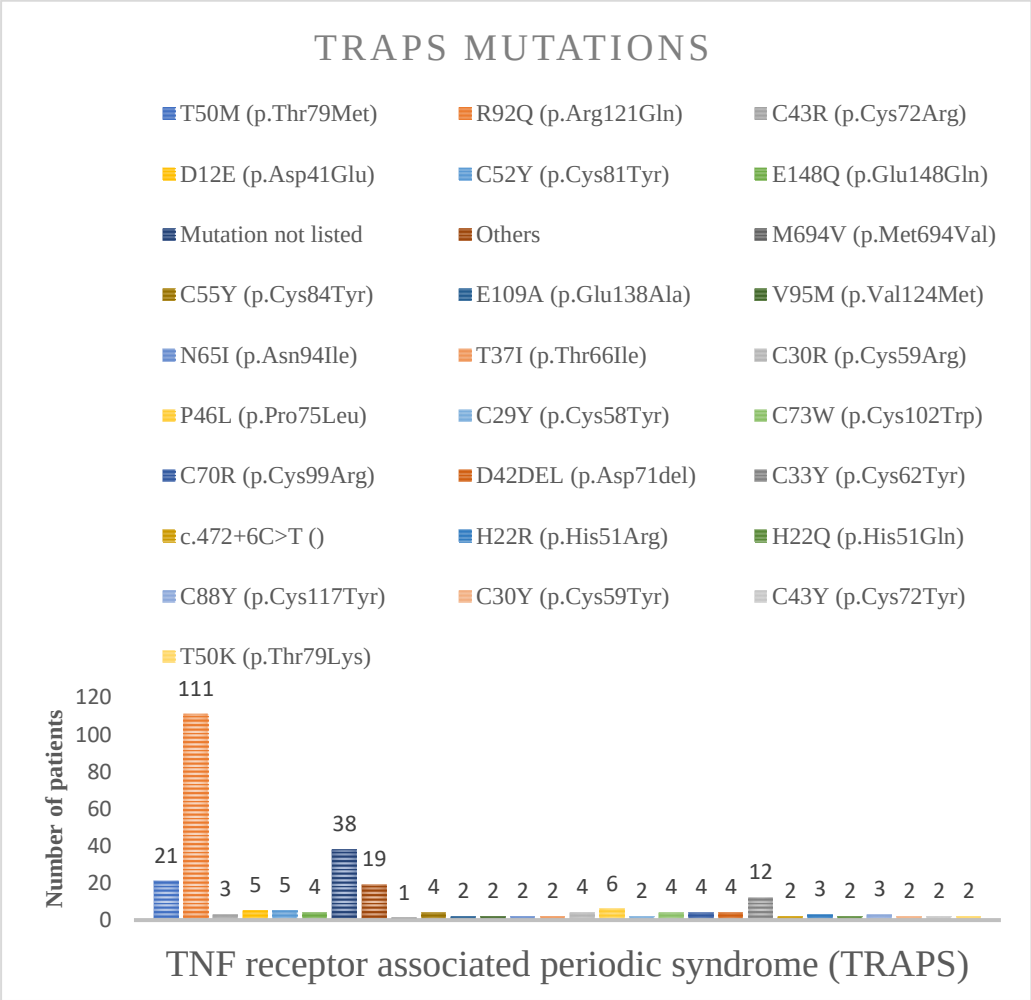


Figure 17: Number of patients carriers of TNFRSF1A gene mutations

Disease	Gene involved	Number of Patients	Number of Total Mutations	Number of Validated Mutations	Number of pathogenic/likely pathogenic Mutations	Number of Benign/likely benign Mutations
TRAPS	TNFRSF1A	225	40	36	31	3
TRAPS	MEFV	6	3	3	1	0
TRAPS	NLRP3	2	2	1	0	0

Table 10: Number of patients carriers of TNFRSF1A gene mutations

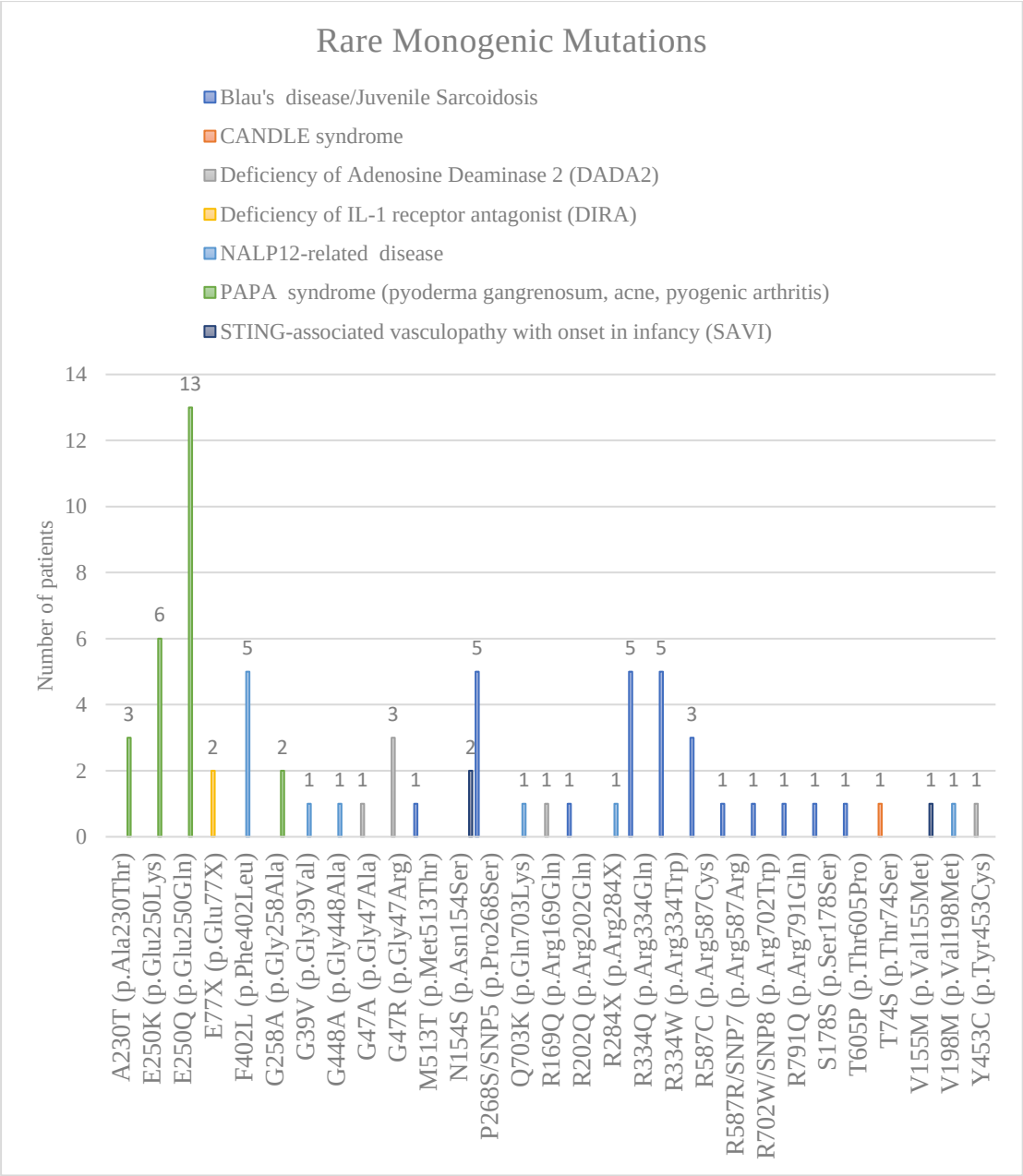


Figure 18: Number of patients carriers of rare monogenic mutations

4.5 Treatment and safety

489 patients have been treated with at least one biologic drug, 1031 with DMARDs, 427 with systemic steroid and 686 with others drugs.

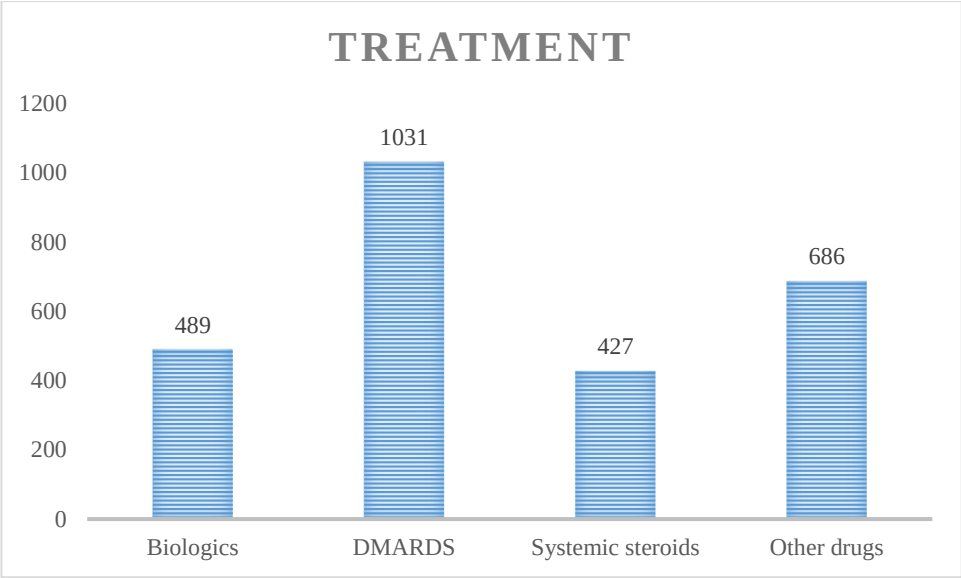


Figure 19: Number of patients treated with different drugs (Biologics, DMARDS, Steroids, Other drugs)

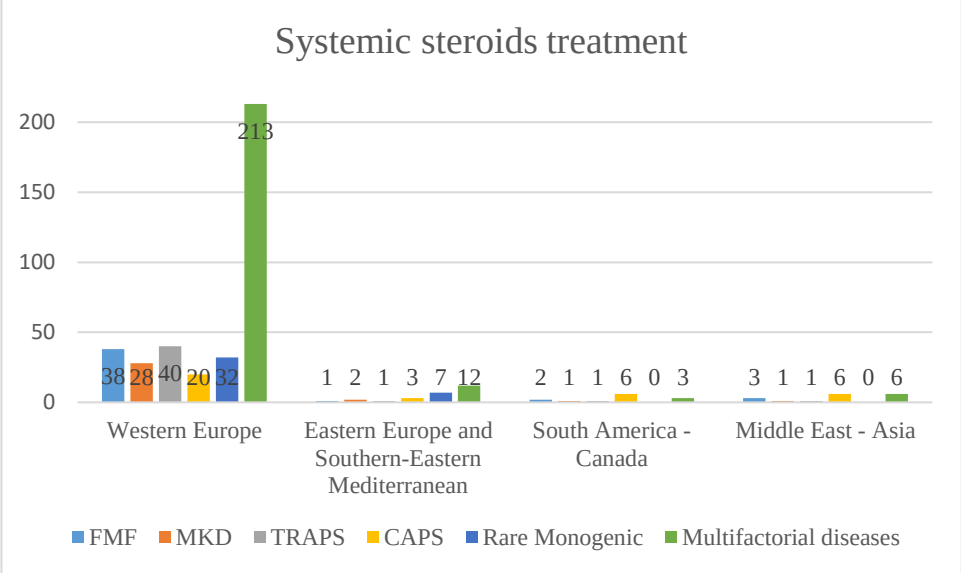


Figure 20: Geographic distribution of patients treated with systemic steroids

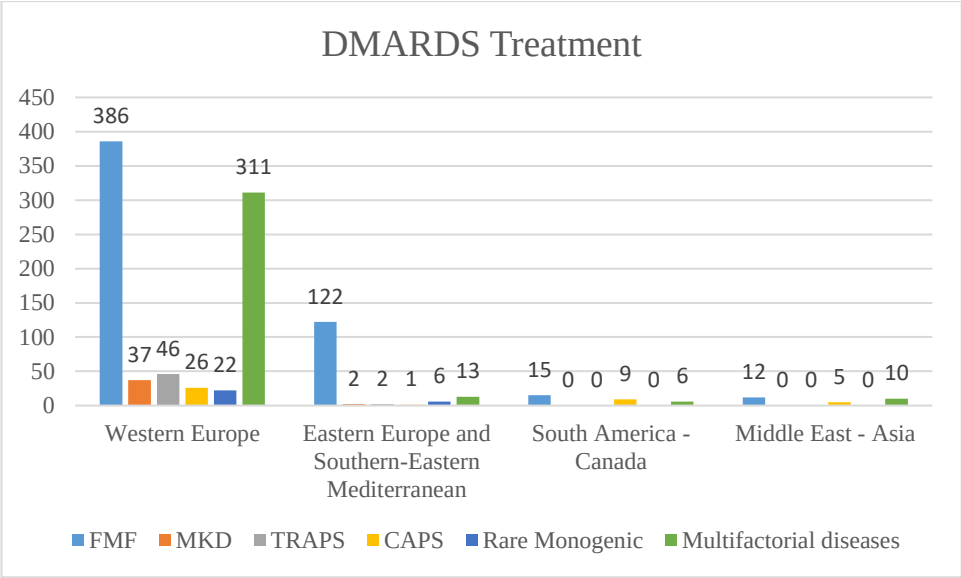


Figure 21: Geographic distribution of patients treated with DMARDS

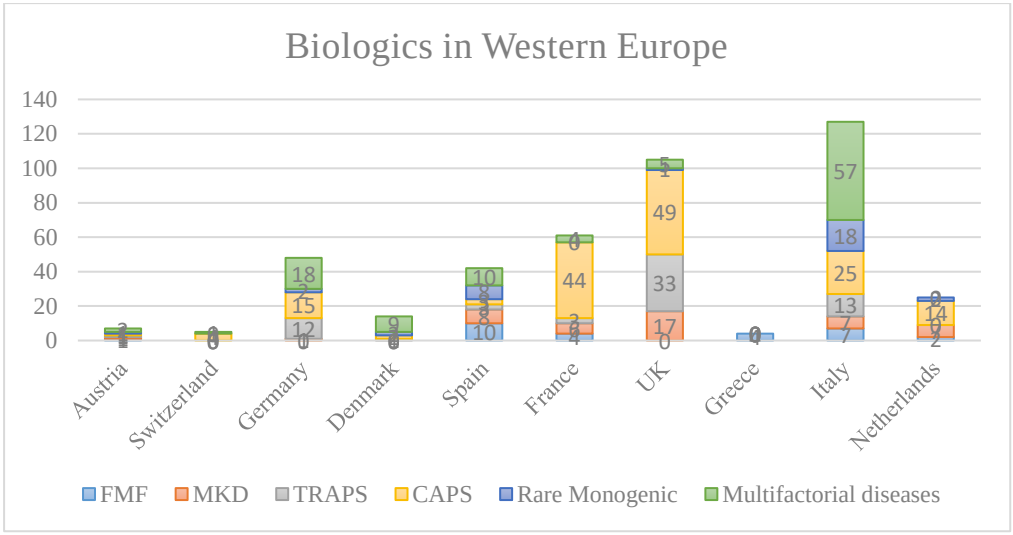
Biologic Drugs

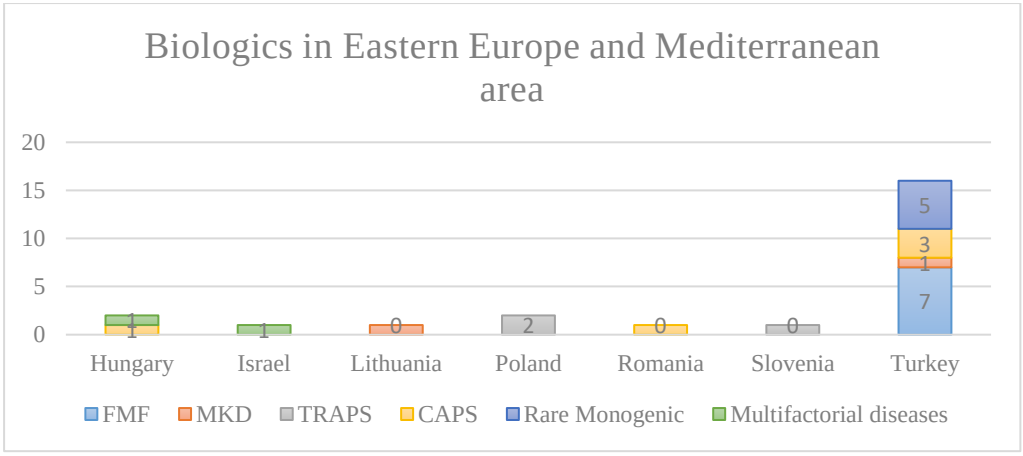
22% of patients enrolled in the Eurofever registry has been treated with biologic drugs . Among these patients, 26% are Italian. The most frequent diseases treated with biologic drugs are (Table 11): CAPS (38%), multifactorial diseases (22%, in particular 9% CRMO, 5% Behcet, 5% Undefined Periodic Fever, 3% Schnitzler), TRAPS (14%), MKD (11%), rare monogenic (8%: one CANDLE patient, 2 DIRA, 2 NALP12, 3 Mayeed, 8 DADA2 and 14 PAPA), and FMF (7%).

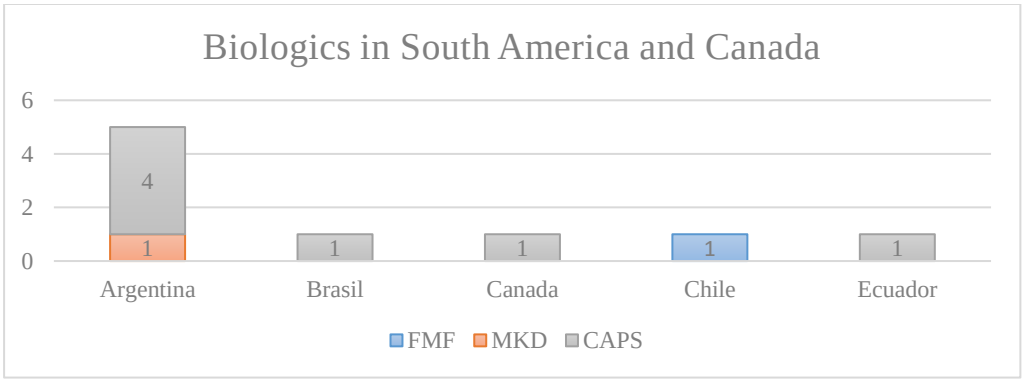
The following figures display biologic use distribution in the different countries: biologic use is prevalent in Western Europe (most in Italy and UK).

BIOLOGICS DRUGS							
	Multifactorial	**Rare Monogenic**	**CAPS**	**FMF**	**MKD**	**TRAPS**	**Total**
Armenia							0
Argentina			4		1		5
Austria	2	1	1	1	1		6
Australia			1				1
Bulgaria							0
Brasil			1				1
Canada			1				1
Switzerland	1		4				5
Chile				1			1
Czech Rep.		1	7		1		9
Germany	18	2	15		1	12	48
Denmark	9	2	2			1	14
Ecuador			1				1
Spain	10	8	3	10	8	3	42
France	4		44	4	6	3	61
UK	5	1	49		17	33	105
Greece				4			4
Croatia							0
Hungary	1		1				2
Israel	1						1
Italy	57	18	25	7	7	13	127
Japan			4				4
Lithuania					1		1
Latvia							0
Netherlands		2	14	2	7		25
Poland						2	2
Romania			1				1
Serbia							0
Russia			2		1	1	4
Saudi Arabia			1				1
Slovenia						1	1
Turckey		5	3	7	1		16
Total	**108**	**40**	**184**	**36**	**52**	**69**	**489**

Table 11: Geographic distribution of patients treated with biologic drugs







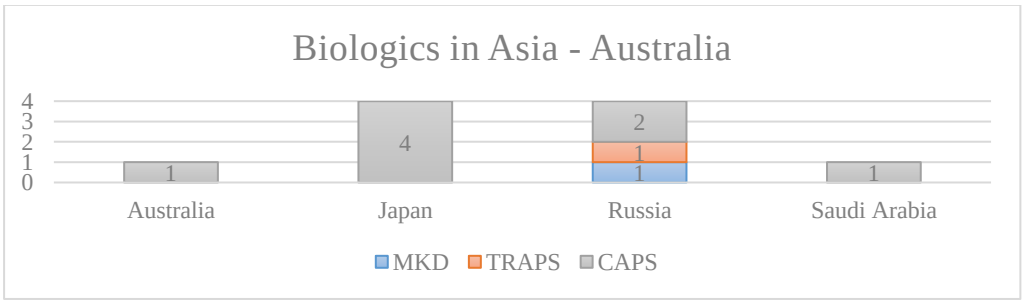


Figure 22: Geographic distribution of patients treated with biologics

4.6 Eurofever Impact on Scientific Comunity

During its first 10 years, the Eurofever registry provided 12 papers with 800 citations. The main new information coming from the registry can be summarized as follows:

- 4.6.1 Insights on the clinical presentation, disease course, complications and response to treatment for the most common autoinflammatory diseases, providing the largest series available in the literature
- 4.6.2.Detailed information on genotype-phenotype correlations in hereditary periodic fever syndromes
- 4.6.3 Evaluation of the accuracy of previous diagnostic criteria and development of new evidence-based classification criteria
- 4.6.4 Development and validation of novel instruments for the management of autoinflammatory diseases in daily practice

4.6.1 Insight on autoinflammatory diseases

The first analysis of the demographic data coming from the Eurofever registry was performed by Toplak et al, in 2012.[5] This report gave the first overview of the distribution of these rare monogenic conditions based on the collection of 1880 patients from 67 centers in 31 countries. Most of the patients (74%) lived in western Europe, 16% in the eastern and southern Mediterranean region (Turkey, Israel, North Africa). Only 6% of the patients were from eastern European countries, highlighting the possibility of a lack of recognition of these diseases or lack of resources in some less economically developed countries. The study was able to analyze the impact of diagnostic delay in these conditions. The median diagnosis delay was 7.3 years (range 0.3-76), with an encouraging

reduction in the time to diagnosis in patients born after the identification of the first gene associated with autoinflammatory diseases (*MEFV* for FMF) in 1997.[9]

Familial Mediterranean fever (FMF)

The homogeneous collection of pediatric patients with FMF coming from different countries and ethnicities enabled for the first time an analysis of the impact of ethnic, environmental and genetic factors on the severity of disease presentation. For this aim, demographic, genetic and clinical data from pediatric patients with FMF enrolled in the Eurofever registry were analyzed. Patients were divided into three subgroups: (i) patients living in the eastern Mediterranean countries; (ii) patients with an eastern Mediterranean ancestry living in western Europe; (iii) Caucasian patients living in western European countries.[10]

The study was conducted on 346 pediatric patients with FMF from 64 centers in 28 countries. European patients had a lower frequency of the high penetrance M694V mutations and a significant delay of diagnosis ($p<0.002$). The study confirmed in the pediatric setting that patients living in the eastern Mediterranean display a more severe disease presentation with a higher frequency of fever episodes per year, more frequent arthritis, pericarditis, chest pain, abdominal pain and vomiting compared to the other two groups. A multivariate analysis was able to confirm that beside the presence of the M694V mutation and a positive family history, the country of residence (eastern Mediterranean countries) was a variable independently associated with severity of disease presentation.

Cryopyrin-associated periodic syndromes (CAPS*)*

Levy et al,[11]evaluated genetic, demographic and clinical features in patients with CAPS from the Eurofever registry. This study was based on the collection of 136 CAPS patients enrolled in the registry with a median onset at age 9 months, median diagnosis at age 15 years and median follow-up duration of 15 years. A heterozygous germline mutation was found in 133 patients, while no mutation was identified in 3 patients. Thirty-one different *NLRP3* mutations were recorded, 7 of which represented 78% of all the patients. More than half of the patients (57%) displayed a chronic disease course, while 43% of the patients were characterized by recurrent episodes. Fever, cutaneous and musculoskeletal involvement were the most prevalent manifestations. Neurological involvement was observed in 55 (40%) patients, with severe involvement in 16 (12%). Ophthalmological involvement was found in 71% of cases and sensorineural hearing loss in 42%. AA amyloidosis was detected in five patients (three carrying a R260W mutation, one V198M mutation and one A439 V mutation).

The authors also analyzed the correlation between genotype and phenotype in this cohort. They found that the T348M variant was associated with a more severe disease course, characterized by early onset, chronic course and neurological involvement. Patients with Q703K polymorphism had a milder disease. Results from this study led to a better understanding of risk factors, prognosis and genotype-phenotype associations in CAPS patients. These findings may have an important impact on therapeutic decisions and on the management of these patients.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS)

In 2013 Lachmann et al,[12] described genetic findings, demographic features and clinical presentation of TRAPS in patients from the Eurofever/Eurotraps international registry. This study, the largest series of TRAPS patients, enrolled 158 patients with a median onset age of 4.3 years; median diagnosis age was 25.9 years and median follow-up duration was 15.6 years.

The most common *TNFRSF1A* variant found in 54 patients (34% of cases) was R92Q (a low-penetrant variant), followed by T50M (10%). Regarding clinical features, the disease course was recurrent in 139 (88%) patients, with episode duration of more than 14 days in 25% of cases. About half of the patients (43%) displayed attacks of 7-14 days. The most common symptoms besides fever were limb pain (85%), abdominal pain (74%), rash (63%) and eye manifestations (45%). AA amyloidosis was noted in 16 (10%) patients at a median age of 43 years. This large series of patients enabled the description of molecular and clinical features of TRAPS syndrome, with emphasis on different phenotype among low-penetrant and pathogenic variants.

Mevalonate kinase deficiency (MKD)

Ter Haar et al,[13] evaluated the phenotype, genotype and response to treatment of patients with MKD enrolled in the registry. Complete information on 114 patients with MKD from 31 centers in 12 countries were available. The median onset age was 0.5 years, median age at diagnosis 6.5 years and median follow-up period was 11.5 years. The disease was characterized by recurrent episodes in 99/114 (87%) patients, with most patients being well between

attacks; however, 10-20% displayed constitutional symptoms between fever episodes such as malaise (61%), fatigue (61%) and weight loss (1%). Gastrointestinal symptoms were observed in almost all the patients (98%).Other main features of this series were mucocutaneous involvement in 87% of patients, lymphadenopathy in 89% and musculoskeletal symptoms in 78%.

Regarding neurological involvement, headache was reported as the most common symptom (38%).The main complication was AA amyloidosis, which developed in 5 (4%) patients, more often in those with p.V377I/p.I268T compound heterozygosity. The most common mutation emergent from the analysis was p.V377I; 84% of the patients had at least one p.V377I mutation.

Treatments used included nonsteroidal anti-inflammatory drugs (NSAIDs) given to 66 (58%) patients, which relieved symptoms in 48 (73%) of them. Corticosteroids given during attacks were completely effective in resolving inflammatory episodes in 19/49 (39%) patients with a partial response in 21/49 (43%). Biologic agents (anakinra, canakinumab and etanercept) were able to induce a complete response in many patients. Specifically, anakinra was administered to 8 patients only during attacks (5 with complete response, 3 with partial response) while 19 patients received anakinra as maintenance treatment; 13 patients obtained a complete remission, while 3 had a partial response.

Chronic non-bacterial osteomyelitis (CNO)

Recently, the first report on patients with CNO collected in the Eurofever registry has been reported.[14] Complete information on 486 patients was available, representing the largest series reported to date. The mean age at onset was 9.9 years (range 1-17.7 years). Adult onset was observed in 31 (6%) patients.

The mean time from disease onset to final diagnosis was 1 year (range 0-15 years).

At baseline, all patients displayed musculoskeletal symptoms with 431 (89%) patients reporting bone pain, 302 (62%) arthralgia, 58 (12%) myalgia, 72 (15%) monoarthritis, 54 (11%) oligoarthritis and 10 (2%) polyarthritis. Nineteen percent of the patients had mucocutaneous manifestations (5% acne, 5% palmo-plantar pustulosis, 4% psoriasis, 3% papulo-pustular lesions, 2% urticarial rash), 8% displayed gastrointestinal symptoms. Among imaging techniques, MRI was performed at baseline in 426 (88%) patients, revealing a mean number of 4.1 lesions. Overall, 37% of patients displayed metaphyseal lesions, 23% epiphyseal, 15% diaphyseal, 25% pelvic, 23% vertebral, 19% clavicle, 15% tarsal, 10% thoracic, 3% carpal and 3% cranial. Bone biopsy was performed in 281 (58%) patients.

Three hundred and sixty-one (74%) patients were treated with NSAIDs, 112 (23%) with corticosteroids, 61 (13%) with bisphosphonates, 58 (12%) with methotrexate, 47 (10%) with sulfasalazine, 26 (5%) with anti-TNF and 4 (1%) with anakinra, with a variable response to all these treatments. However NSAIDs, bisphosphonates and sulfasalazine displayed the highest rate of complete or partial response.

The study showed that CNO often presents during early adolescence and the range of clinical manifestations and response to treatment is heterogeneous

4.6.2 Genotype-phenotype correlations

The large number of polymorphisms and common variants in hereditary recurrent fever (HRF) genes makes it difficult to find associations between genotype and phenotype. The Infevers database collects all these variants and

provides a brief description of clinical manifestations of the first patient reported for each mutation. With the aim of improving knowledge of genotype-phenotype correlations, Papa et al,[15]in a recent study, developed an open web-based registry of genotype-phenotype associations derived from all the patients with HRF enrolled and validated in the Eurofever registry

4.6.3 Development of new classification criteria

As mentioned previously, one of the main purposes of the Eurofever registry was to generate evidence-based diagnostic and classification criteria. Formal diagnostic criteria have been developed for some inherited periodic fevers (FMF and CAPS), based on the main clinical manifestations associated with the specific disease within the context of limited populations. Thus, there is a question of their generalization to other populations.[16, 17]

Therefore, the large Eurofever registry was used to test the accuracy of different diagnostic criteria currently in use for FMF and compared them with the performance of previous criteria for the diagnosis of familial Mediterranean fever (FMF).

The performances of the Sohar Tel Hashomer, Livneh Tel-Hashomer, and Yalcinkaya FMF criteria were assessed in pediatric patients with FMF compared to other periodic fevers, including MKD, TRAPS, CAPS, PFAPA and undefined periodic fever from the same registry.[18]

The FMF group included 339 patients whereas the control group consisted of 377 patients (53 TRAPS, 45 MKD, 32 CAPS, 160 PFAPA and 87 undefined periodic fevers). Patients with FMF were correctly diagnosed using the Yalcinkaya criteria with a sensitivity rate of 87.4% and a specificity rate of 40.7%. On the other hand, the Sohar Tel Hashomer and Livneh Tel-Hashomer

criteria displayed a sensitivity of 45.0 and 77.3%, respectively. Both latter criteria displayed a better specificity than the Yalcinkaya criteria: 97.2 and 41.1% for the Sohar Tel Hashomer and Livneh Tel-Hashomer criteria, respectively. The overall accuracy for the Yalcinkaya criteria was 65 and 69.6% (using 2 and 3 criteria), respectively. Ethnicity and residence had no effect on the performance of the Yalcinkaya criteria.

Thus, the pediatric Yalcinkaya criteria yielded a better sensitivity than the other criteria in this international cohort of patients. However, the specificity was lower than the previously suggested adult criteria.

In 2015 Federici et al,[19] developed and validated a new set of clinical criteria for the classification of patients affected by the four main autoinflammatory recurrent fever syndromes. Patients with HRF (FMF, MKD, TRAPS and CAPS) enrolled in the Eurofever Registry until March 2013 were evaluated. Patients with PFAPA syndrome were used as negative controls. The 'gold-standard' for diagnosis of the monogenic diseases was based on the presence of a confirmatory genetic analysis.[20,21]Patients with non-confirmatory genetic analysis, such as low-penetrance mutations, were excluded from the study. Patients with PFAPA were classified according to current diagnostic criteria.[22]

Twelve hundred and fifteen patients enrolled in the registry were analyzed: 518 were selected as the 'gold standard group' (291 FMF, 74 MKD, 86 TRAPS and 67 CAPS) and 119 patients with PFAPA were evaluated as the negative controls. The authors randomly divided the 'gold standard group' into two subgroups. Univariate and multivariate analyses were performed in the first training set subgroup (412 patients) to identify clinical variables which strongly correlated with each disease. The second validation subgroup (305 patients) was used to assess the performance of the 4 scores originated from statistical analysis in an

independent group of patients. All criteria displayed a high sensitivity and specificity (Table 2).

This study facilitated the development of a validated evidence-based tool that may be useful either as an indication for performing genetic testing or for clinical classification of patients with suspected autoinflammatory periodic fevers.

4.6.4 Validation of disease activity and damage scores

As previously stated, the main outcome measure in therapeutic trials is the disease activity. However, validated indices of disease activity were lacking before the creation of the registry. Development and validation of these activity parameters represented another aim of the Eurofever project.

The first index of activity (Autoinflammatory Diseases Activity Index, AIDAI) was proposed in 2013 for patients affected by the four major HRF syndromes: FMF, MKD, TRAPS and CAPS .[23]

This study was initiated in November 2010 by an international collaboration of eight centers belonging to the PRINTO/Eurofever network. They established the content of a disease activity tool for HRFs and started with the enrollment of consecutive patients attending participating centers. Each patient had to complete a 1-month prospective diary before a scheduled clinical appointment during which the physician assessed the disease activity by a questionnaire. Data coming from the various centers were centrally collected in the Eurofever database and then eight international experts in autoinflammatory diseases evaluated the patients' disease activity by a blinded web evaluation. The second step of score validation was a consensus conference where the experts evaluated the level of disease activity. The last step of the study was the calculation of the score to discriminate active from inactive disease by statistical analysis.

One hundred six patients were enrolled (42 FMF, 39 CAPS, 14 TRAPS and 11 MKD). During the second step of the validation process, consensus was achieved for 98/106 (92%) cases (39 FMF, 35 CAPS, 14 TRAPS and 10 MKD); 26 patients were declared to have inactive disease and 72 had active disease, with different grades of activity (low-mild-severe). Statistical analysis performed with receiver operating characteristic (ROC) curve revealed that an AIDAI cut-off score ≥9 discriminated active from inactive disease with the best accuracy (sensitivity of 89% and specificity of 92%).

After this first study, a damage index score (Autoinflammatory Disease Damage Index, ADDI) was developed in 2016 by Ter Haar at al,[24] for FMF, CAPS, TRAPS and MKD . The top 40 enrollers of patients in the Eurofever registry and 9 experts from the Americas participated in multiple rounds of online surveys to select items and definitions of damage. Also 22 patients or parents of patients were invited to participate in an online survey. Authors used the 1000minds software to assess the scoring system of ADDI with the correct weight to each damage item. The online surveys were completed by >80% of experts, who suggested 16 new damage items. The next step of the index assessment was a consensus meeting, which was attended by 31 experts. During this meeting, items that didn't reach consensus in the online survey were discussed. At the end of this process, the preliminary ADDI score contained 18 items, classified in the following categories: reproductive, renal/amyloidosis, developmental, serosal, neurological, ears, ocular and musculoskeletal damage, each with a different weight. The highest weight was attributed to renal and neurological categories. Authors highlighted the strength of this index score, due to the number of experts that attended the survey and to the involvement of patients or parent of patients.

Chapter 5 - DISCUSSION

In the present study we purpose to highlight the support of Eurofever project for identification and characterization of AIDs. The main features of a successful international registry are a widespread involvement of international Centers and a continuous updating from enrolling centers. The first demographic study of Toplak et al[5](2012) was based on analysis of the first 1880 enrolled patients, coming from 31 Countries. The present study analyzes the enrollment during the first ten years of the registry and it represents a great opportunity for knowledge of these rare diseases, with the collection of data from almost 4000 patients all over the world. In the last years we have observe an encouraging increase of involved Countries, with a greater number of patients coming from geographic area, poorly represented in the first epidemiologic study of Toplak et al. Interestingly, we have observed an increase of 2 % of patients enrolled in Eastern-Europe and of 3 % in Asian Countries. These findings suggest a progressive improvement of knowledge of these rare disorders also in emerging Countries and with limited access to genetic analysis. The analysis of Eurofever data confirm that most of patients affected by AIDs present a disease onset during pediatric age, underlining the importance of an early diagnosis. A relevant part of patients (405 patients, 12% of total population) presented a pediatric onset, but received diagnosis only in adult age. Diagnostic delay represents a major issues for rare diseases. Complications of non-treated disease (amyloidosis, kidney insufficiency, earing-loss, mental delay etc) represent an increased risk of morbility and long term irreversible damage. Eurofever data analysis has confirmed an improvement of diagnostic ability during the last years, with a reduction of mean diagnostic delay.

Besides these data, the registry highlighted as almost 10% (334) of enrolled patients presented disease onset during adult age; these patients are not only patients affected by multifactorial disorders, but also affected by monogenic diseases (like CAPS and TRAPS). In these last cases the mutations detected are polymorphism or variants with low penetrance (compared to the total of adult patients with validate mutations, 16% of CAPS and 23% of TRAPS present pathogenic variants of likely pathogenic). Regarding the pattern of frequency of diseases, for monogenic periodic fevers (TRAPS, FMF, CAPS, MKD) a variable percentage of patients presents a chronic course (typically in severe forms of CAPS and MKD). To date, in the registry detailed data about clinical manifestations are available for 88% of patients.

Finally, the Eurofever registry allowed the analysis of global therapeutic approach for autoinflammatory diseases. The use of NSAIDs, steroid on demand and Colchicine still represents the most used approach. The use of biologics represents a new opportunity for the treatment of AIDs; data coming from Eurofever highlight how biologics are mostly used in developed countries, while their use in emerging countries is still limited. In the present study, we have evaluated the impact of the Registry on Scientific Community; during its first 10 years, the Eurofever registry provided 12 papers with 800 citations. Detailed analysis of clinical features collected in Eurofever database allowed to perform studies with large cohort of patients[10,11,12,13,14],to purpose new classification criteria[19], to validate damage and activity score and to evaluated genotype/phenotype correlation[15]. At the beginning of the project, the Eurofever database collected exclusively data from disease onset to diagnosis, based on retrospective information collected during the first visit at referred Center. During the following years, it was clear the need to establish a register able to

observe the long-term evolution of diseases, the compliance and efficacy of different therapeutic approach. In February 2015 we started the longitudinal collection of data, with a particular focus on treatment and safety. To date, longitudinal data are available for about 12% of enrolled patients. The enrollment of patients in Eurofever Registry is still ongoing. The creation of a large cohort of follow-up data, with focus on treatment and safety, will allow a better knowledge on natural history of these rare diseases, improving the management of patients affected by these conditions. In conclusion, during this first 10 years, the international effort to build a common registry on autoinflammatory diseases led to a considerable accumulation of new information, concerning the modality of presentation, disease course, genotype-phenotype correlations and response to treatment in rare inflammatory conditions. New tools for every-day practice have been also developed with an evidence-based approach coming from real patients enrolled in the registry. Studies on other rare and newly recognized conditions (such as DADA2 and interferonopathies) are currently ongoing. Long-term studies will help understand the efficacy and safety of different treatments used in these rare conditions.

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