Rheumatology Advances in Practice, 2023, **7**(1), rkad001
https://doi.org/10.1093/rap/rkad001
Advance access publication 9 January 2023
Concise report

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Spectrum of auto-inflammatory diseases in Morocco: a monocentric experience

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Abstract

Objective: Auto-inflammatory diseases (AIDs) result from mutations in genes of the innate immune system leading to periodic multisystemic inflammation. We aimed to describe the clinical, biological and molecular features (when available) and outcomes of Moroccan patients with AIDs.

Methods: Patient data were collected retrospectively and analysed over a 13-year period.

Results: Among 30 patients, 60% had FMF, 16% mevalonate kinase deficiency (MKD) and 24% other AIDs. The mean age at first consultation was 6.9 years, and the mean diagnostic delay was 3 years. Consanguinity was reported in 16 cases. IgA vasculitis was associated with 33% of FMF patients, in whom the main clinical features were fever (88.8%), abdominal pain (100%), arthralgias (88.8%) and arthritis (50%), and the most frequent mutation was M694V (66%). All FMF patients were treated with colchicine. Most MKD patients were confirmed by elevated urinary mevalonic acid levels, and four of five MKD patients received targeted therapy. Chronic recurrent osteomyelitis patients were confirmed by radiological and histological analysis. Two cases of Marshall syndrome were diagnosed according to validated criteria. A case of familial pustular psoriasis was diagnosed based on histological analysis and a patient with Muckle–Wells syndrome by clinical features. The outcome was favourable in 76%, partial in 13%, and three deaths were reported.

Conclusion: FMF and MKD are the most reported diseases. AIDs are probably underestimated because they are unknown to clinicians. The aim of this work is to raise awareness among paediatricians about AIDs and create a network for best practice.

Lay Summary

What does this mean for patients?
Autoinflammatory diseases (AIDs) are rare disorders caused by mutations in the genes of the immune system. We carried out a retrospective analysis of data from Moroccan patients with AIDs in a paediatric rheumatology unit. We found a high rate of the M694V genetic mutation in these patients owing to marriage between blood relatives, which is common in Moroccan culture. Patients from such marriages are likely to have inherited genetic diseases, such as familial Mediterranean fever, followed by mevalonate kinase deficiency in our cohort. This study represents the first experience of AIDs in Morocco. Diagnosis of AIDs is based primarily on clinical and biological signs, because genetic tests are not widely available. This study aims to raise awareness of AIDs among paediatricians and help to promote better disease management. This will enable an earlier diagnosis and help to improve the prognosis of the patients.

Keywords: auto-inflammatory diseases, FMF, mevalonate kinase deficiency, genetics, children

Key messages

- FMF is the most frequent disease in our study owing to the high rate of consanguinity.
- The M694V mutation is the most identified among our FMF patients.
- Specific clinical and paraclinical features are crucial points on which to base the diagnosis in the absence of availability of genetic testing.

Received: 20 July 2022. **Accepted:** 10 November 2022

Introduction

Auto-inflammatory diseases (AIDs) are conditions caused by dysregulation of the innate immune system involving mutations in genes encoding innate immunity proteins. They are characterized by a stereotypical clinical picture of episodic fever with symptom-free intervals and biological signs of systemic inflammation [1]. Currently in Morocco, owing to the lack of a national registry of AIDs, the frequency and prevalence of these diseases are still unknown and probably underestimated. In this study, we share the details of this first single-centre Moroccan cohort.

Methods

Local registry

The first centre specialized in the diagnosis and management of AIDs was the Paediatric Rheumatology Unit of the Mother and Child University Hospital in Casablanca, Morocco. Since its inception, this centre has received patients from paediatricians working in other public hospitals and private clinics. This informal registry was designed to provide an epidemiological picture of AIDs in Casablanca in the absence of a national registry in Morocco.

Data collection

We carried out a retrospective analysis of patients' clinical and biological data and genetic tests for a period of 13 years (2006–2019). For each patient, a standardized form was drawn up and duly completed by the physician responsible for the patient's care, then validated by an AIDs expert. The data collected from the medical records included personal information, clinical signs and results of additional tests, therapeutic management and follow-up.

Patient consent and ethics

For studies involving human participants, all procedures performed conformed with ethical standards of the institutional ethics committee of the University Hospital Center Ibnou Rochd (2021/DOEHRSI/31, file no. 03/2) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Given the nature of this retrospective work, informed consent for participation in this study was not required. However, written informed consent for genetic testing as part of the patient's therapeutic care was obtained from the patient's parents.

Diagnosis and classification of patients

Patients were diagnosed based on recurrent febrile attacks separated by symptom-free intervals. They were classified according to the following inclusion criteria: more than three episodes of recurrent fever and CRP >40 mg/l, after exclusion of immune deficiencies, autoimmune diseases, neoplasia and infectious diseases [2]. Commonly used inflammatory biomarkers were ESR, CRP and serum amyloid A protein. Specific biochemical tests, including urinary mevalonic acid, and genetic tests were performed regarding the clinical setting. Patients were categorized according to the PRINTO–Eurofever criteria and the results of the biological and genetic analyses, except for one patient with the full clinical form of Muckle–Wells syndrome. Complete remission was considered in the event of absence of clinical symptoms and the inflammatory syndrome. Partial remission was defined by absence of clinical signs but persistence of a moderate inflammatory syndrome.

Data analysis

Statistical tests including mean proportions, minimum and maximum values were used for descriptive analyses and performed using Microsoft Excel v.14.0.

Results

Epidemiological data

Thirty patients of Moroccan origin were referred to our unit for recurrent fever. The average age at first consultation was 6.9 years (range, 8 months to 14 years), and the average age at the onset of symptoms was 4.9 years (range, 5 months to 13 years). The mean diagnostic delay was 3 years (range, 1 month to 12 years).

The age distribution showed a predilection for children between 2 and 13 years old (Supplementary Table S1, available at *Rheumatology Advances in Practice* online), with a male-to-female sex ratio of 1:1. Consanguinity was reported in 16 cases, of which 13 were of first degree, two of second degree, one of third degree, and unknown in one case of an adopted child.

The distribution of patients was as follows: 18 cases of FMF, 5 cases of mevalonate kinase deficiency (MKD), 3 patients with chronic recurrent multifocal osteomyelitis, 2 cases presenting a characteristic phenotype of Marshall/periodic fever, aphtous pharyngitis, adenitis (PFAPA) syndrome, 1 patient with familial pustular psoriasis and 1 patient with Muckle–Wells syndrome.

Clinical and paraclinical findings

The frequency of the attacks varied according to the AID type and even within the same disease. Tables 1 and 2 summarize the clinical and paraclinical data of patients with AIDs in our unit.

Therapeutic and evolutive parameters

All patients with FMF received colchicine at 0.5 mg/day for patients <5 years of age, 1 mg/day for patients between 5 and 10 years, and 1–2 mg/day for patients >10 years depending on the clinical and biological response, with complete remission in 14 cases; combined with NSAIDs (ibuprofen at 40 mg/kg/day) in 6 cases, corticosteroids at 0.5–1 mg/kg/day in 6 cases, and paracetamol at 60 mg/kg/day in 2 cases on demand. Partial remission was reported in three cases. An unexplained sudden death occurred in the adopted FMF patient. PFAPA syndrome patients with the uncertain pathogenic heterozygous mutation E148Q were treated with colchicine in a similar manner to FMF patients, after one dose of corticosteroids 1–2 mg/kg and/or ibuprofen failure. One of them received anakinra with success.

Regarding MKD, four patients received targeted therapy: with anakinra 2–5 mg/kg/day in three cases, marked by a spectacular improvement in two cases and failure in the other one, which required switching to corticosteroids and ciclosporin A at 5 mg/kg/day, with death from severe macrophage activation syndrome. The fourth patient was treated with etanercept 0.8 mg/kg/week resulting in a good response but was loss to follow-up. The fifth patient with MKD received ibuprofen 40 mg/kg/day on demand after failure of a colchicine

Table 1. Epidemiological data and clinical signs of patients with autoinflammatory diseases

Data	FMF	MKD	CRMO	PFAPA	MWS	FPP
Patients, *n*	18	5	3	2	1	1
Sex, *n* (♀/♂)	11/7	3/2	1/2	1/1	0/1	0/1
Age at onset of symptoms, mean (range)	5 years (10 months to 13 years)	2 years and 4 months (5 months to 6 years)	6 years (4–10 years)	8 years and 1 month (14 months to 7 years)	4 years	7 years
Age at first consultation, mean (range)	6 years (17 months to 15 years)	6 years and 6 months (8 months to 14 years)	11 years 6 months (10–13 years)	7 years (3 years and 4 months to 11 years)	4 years and 2 months	8 years
Mean diagnostic delay	1 year and 6 months	5 years and 9 months	4 years 8 months	1 year	12 years	1 month
Consanguinity, *n*	10	3	2	–	1	–
Fever, *n* (average temperature, °C)	16 (39–40)	5 (39.5)	3 Not determined	2 (39)	1 (38.5–39)	1 (40)
Abdominal pain, *n*	18	5	1	2	+	–
Diarrhoea, *n*	4	1	–	–	+	–
Vomiting, *n*	9	1	–	–	+	–
Arthritis, *n*	9	3	1	–	+	–
Arthralgia, *n*	16	3	2	2	+	+
Axial involvement, *n*	1	–	1	–	–	–
Myalgia, *n*	1	1	–	–	–	–
Chest pain, *n*	6	–	–	1	+	–
Pseudo-erysipela, *n*	1	1	–	–	–	–
Urticaria, *n*	2	1	–	–	+	–
Aphtous, *n*	4	4	–	1	–	–
Headache, *n*	4	–	–	–	–	+
Adenopathy, *n*	4	5	–	2	–	+
Hepatomegaly, *n*	–	1	–	–	–	–
Splenomegaly, *n*	–	4	–	–	–	–
Other signs, *n*	–	Growth delay (1)	–	Otitis Pharyngitis (1)	Deafness, mutitis, conjunctivitis, peritonitis Severe vasculitis Purulent otitis	Pustulosis Family case Scaly lesions Palmoplantar keratoderma Nail finger lesions
Death, *n*	1	1	0	0	1	0
Cause of death	Unexplained sudden death	Severe macrophage activation syndrome			Alveolar pulmonary haemorrhage	

CRMO: chronic recurrent multifocal osteomyelitis; FPP: familial pustular psoriasis; MKD: mevalonate kinase deficiency; MWS: Muckle–Wells syndrome; PFAPA: periodic fever, aphtous pharyngitis, adenitis.

test at maximal dose of 1 mg/day for a 5-year-old girl with a partial response.

Two patients with chronic recurrent multifocal osteomyelitis were treated with adalimumab at 24 mg/m^2/2 weeks, preceded by CS therapy at 2 mg/kg/day and etanercept at 25 mg/week in one case, with complete remission in both cases. The third patient with chronic recurrent multifocal osteomyelitis was treated with NSAIDs (indomethacin 3 mg/kg/day), with partial remission.

The patient with familial pustular psoriasis, from a non-consanguineous family, presented from the age of 8 years a high fever, erythematosquamous lesions, palmoplantar keratoderma and generalized flat pustules. Similar familial cases have been reported (one brother and two sisters). In the absence of anti-IL17, he was treated with anakinra 2 mg/kg/day, then with ciclosporin A 5 mg/kg/day with failure, leading to switching to MTX at 0.5 mg/kg/week combined with etanercept at 0.8 mg/kg/week, resulting in an increase in the period between flares.

The patient with Muckle–Wells syndrome, from a consanguineous marriage and with a similar familial case (sister misdiagnosed with lupus), presented since the first months after birth recurrent fevers associated with sensory disorders (deafness and mute) and severe vasculitis revealed by several episodes of intestinal perforations from the age of 2 years. He also presented cervical adenopathy, abdominal and chest pain, urticaria, arthralgia, myalgia and recurrent red conjunctivitis from the age of 4 years. He received several boluses of methyl prednisolone 1 g/1.73m^2 combined with i.v. CYC 500 mg/m^2/monthly, then prednisone at 5 mg/day and AZA at 3 mg/kg/day for years, with short periods of remission. Anakinra 2 mg/kg/day was tried very late, 2 months before his death at age 15 years after a sudden alveolar haemorrhage.

Discussion

AIDs research is a major challenge because of the rarity of cases. The creation of the two European registries, Eurofever and AID-Net, has provided more epidemiological, clinical and therapeutic data on AIDs. Our study is the first to provide a detailed description of the epidemiology and management

Table 2. Complementary examinations of patients with autoinflammatory diseases

Analysis	Parameter	FMF	MKD	CRMO	PFAPA	MWS	FPP
Biological analysis	Average CRP, mg/l *n*	113.3 11	84.9 4	–	83.3 1	206.0 1	104.8 1
	Average ESR, mm in first 1 h *n*	55.9 13	48.2 5	34.3 1	85.5 1	65 1	73.7 1
	Average serum amyloid A, mg/l *n*	52.0 3	230.5 1	–	175 1	–	–
	Average fibrinogen, g/l *n*	2.2 2	–	–	–	–	–
	Average urinary mevalonic acid, mmol/mol creatinine *n*	–	1385.6 3	–	–	–	–
Radiological analysis		–	–	Radiograhgy: bilateral tibial diaphysis medullary infiltration (1 case) Scintigraphy: locomotor hypercaptation (1 case) CT scan: CRMO-evoking appearance (1 case)	–		
Histological analysis		–	–	Bone biopsy: Sclerotic bone appearance Osteolytic lesions Fibrous sites and inflammatory infiltrates	–	Intestinal biopsy: perforation, causing vasculitis and necrotizing enterocolitis	Skin biopsy: pustular psoriasis, matching pustular and psoriasiform dermatitis
Genetic analysis Type of mutation, *n*		Homozygous M694V, 8 Heterozygous M694V, 4 Heterozygous A744S, 3 Heterozygous K695R, 2 P369S/R408Q, 1	Heterozgous V337I, 1	–	Heterozygous E148Q, 2	–	–

CRMO: chronic recurrent multifocal osteomyelitis; FPP: familial pustular psoriasis; MKD: mevalonate kinase deficiency; MWS: Muckle–Wells syndrome; PFAPA: periodic fever, aphtous pharyngitis, adenitis.

of AIDs in Morocco. Nowadays, new biomarkers allow patients to be classified, but in our country they are not always available in routine practice. Genetic exploration is needed to confirm a diagnosis. The only genetic analyses available in Morocco concern the exon 10 *MEFV* mutations and, exceptionally, in the context of research, exons 2 and 3. The *MVK* mutation was determined in collaboration with an international centre.

Autosomal recessive disorders, such as FMF or MKD, are associated with consanguinity, which is an integral part of cultural and social life in Arab countries, including Morocco. In our study, consanguinity was reported in 53% of patients (16 of 30), which is very similar to a previous Moroccan study on FMF, in which consanguinity was ∼60% (72 of 120) [3]. Moreover, consanguinity was found to be 74.6% in 144 patients with AIDs in a multicentre study by the Arab Paediatric Rheumatology Group, and 28.1% of patients (20 of 71) in a Turkish study [4, 5]. This rate of consanguinity is higher than that found in the general Moroccan population (15.25% in 2009) [3].

Consistent with previously published large cohort studies, our results highlight FMF as the most common disease, while the prevalence of other diseases differs between countries [6] (Table 3). Demographic data from a study of 1880 patients in the Eurofever registry showed that most patients were from Western Europe and the southern Mediterranean region, and the mean time to diagnosis ranged from 2 to 7 years [7]. In our study, the mean time to diagnosis was 3 years, with a range of 1–12 years. Although reported in adults, AIDs usually begin in the early years of life [10]. Our patients had a mean onset of symptoms before the age of 5 years. Furthermore, our study does not differ from the literature, where the most frequent symptoms are fever, abdominal pain and joint involvement [11].

The distinction between these diseases is based on the family history including consanguinity and similar family cases, ethnic and geographical origin, duration of febrile episodes and clinical signs, complemented whenever possible by molecular genetic analysis [2]. The diagnosis of our patients was established according to well-defined criteria, including a

Table 3. Comparative table of AIDs identified in other studies

	Our study	Eurofever registry [7] (2019)	Germany, Austria and Switzerland [8] (2019)	Japan [9] (2018)
Total number of patients	30	4048	54	135
FMF	18	1147	20	22
	60.0%	28.3%	37.0%	16.3%
MKD	5	214	1	–
	16.6%	5.3%	1.8%	–
TRAPS	–	302	1	3
CRMO	3	585	15	–
CAPS	1	348	2	6
FPP	1	–	–	–

CRMO: chronic recurrent multifocal osteomyelitis; FPP: familial pustular psoriasis; MKD: mevalonate kinase deficiency; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome; CAPS: Cryopyrin-Associated Autoinflammatory Syndromes

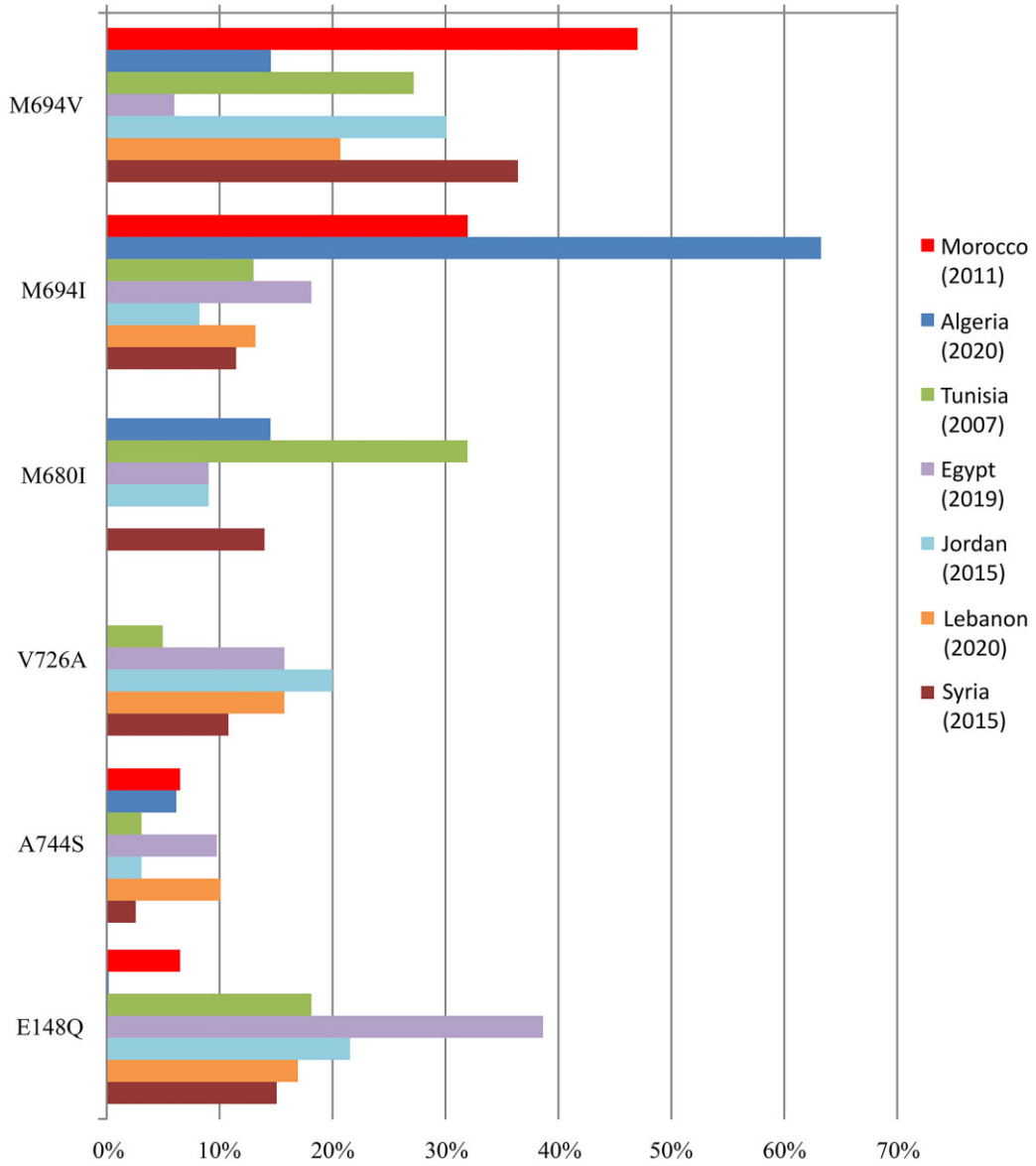

Figure 1. Distribution of mutations frequently reported in the Maghreb and Middle East

stereotypical febrile attack more than three times per year with a symptomless or symptom-poor intercritical period, typical clinical signs, and biological inflammation during the episodes [10]. However, two patients with FMF were included despite the absence of reported fever because they were diagnosed during their hospitalization with IgA

vasculitis, major inflammatory syndrome and refractory abdominal pain, leading to the hypothesis of associated FMF confirmed by genetics.

FMF is significantly the most frequently reported disease in our study, with a preponderance of the M694V mutation, as shown in previous studies in Morocco by Belmahi *et al.* [3] and in other Arab countries (Fig. 1) [12–16]. The association with IgA vasculitis is well known and reported in many FMF series [17]; it was found in 33% of our FMF patients. Colchicine remains the best treatment for FMF [6]. In our study, all patients with FMF were treated with colchicine, with a predominantly favourable response. Studies have reported the presence of *MEFV* mutations in patients with PFAPA syndrome. Our patients with PFAPA phenotype had a heterozygous E148Q mutation of uncertain significance, which was reported with a percentage of 8.3% in a study including 167 PFAPA patients [18]. MKD is the second most common disease in our study, with a relatively long mean time to diagnosis of 6 years but shorter than described in other studies, where it exceeded 10 years [19]. Owing to the lack of genetic testing in Morocco, the diagnosis was based on increased urinary mevalonic acid. As in the Eurofever cohort, where biological agents such as anakinra and etanercept achieved an estimated 89% and 65% complete remission, respectively [6, 7], a complete remission was observed with anakinra in two patients.

Overall, the therapeutic goal is to suppress systemic inflammation. Historically, corticosteroids and colchicine have been used with great benefit. However, there are refractory cases that require targeted therapy, with a preference for anti-IL1 molecules with proven efficacy [7]. In our series, the use of biotherapies gave good results in most cases. In Morocco, bioagents are available but not affordable for all patients. Only patients who are close to major medical centres and have health insurance or a social card issued by the local authorities can benefit from these therapies.

AIDs-related morbidity and mortality remain significant [20]. In our study, the Muckle–Wells syndrome patient died owing to very late initiation of bioagents not available at the onset of his disease, and the MKD patient died owing to development of macrophage activation syndrome, which is a severe complication. In an Indian multicentric cohort, death was reported in 8 of 49 cases, for similar reasons (unavailability of biotherapy or occurrence of complications) [20].

The limitations in our study are as follows: it was a monocentric and retrospective study; the patients included were those with a confirmed diagnosis; patients with recurrent but not labelled fever were excluded; and diagnosis around an index case was not systematic.

Conclusion

Our study highlights the predominance of autosomal recessive AIDs owing to the high rate of consanguinity, in addition to the frequency of delayed diagnosis owing to the lack of awareness of these conditions. In our setting, where genetic tests are not available, the family history, clinical features and inflammatory syndrome are the essential tools that lead to an accurate diagnosis. To improve the diagnosis of AIDs in Morocco, we plan to develop a genetic laboratory and to initiate a training programme through a national network to raise awareness about these diseases in which symptoms are not pathognomonic. To improve prognosis, we also advocate for biotherapy to become affordable for all patients.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

No specific funding was received from any funding bodies in the public, commercial or not-for profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Acknowledgements

All authors contributed to the conception and design of the study, read and approved the final manuscript.

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