original article

A retrospective review of autoinflammatory diseases in Saudi children at a rheumatology clinic

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BACKGROUND AND OBJECTIVE: Published data from Saudi Arabia regarding autoinflammatory diseases are scarce. In this study, we describe the clinical and laboratory features of autoinflammatory diseases in Saudi children.

DESIGN AND SETTING: Restrospective, hospital-based study conducted from January 2010 until June 2010.

PATIENTS AND METHODS: Patients with autoinflammatory disease treated at the Pediatric Rheumatology Clinic at King Faisal Specialist Hospital and Research Center, Riyadh, over the past 10 years were included. Autoinflammatory diseases included the following: familial Mediterranean fever (FMF); chronic recurrent multifocal osteomyelitis (CRMO); early-onset sarcoidosis (EOS); periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA); chronic infantile neurologic cutaneous and articular syndrome (CINCA); and Muckle-Wells syndrome (MWS). Demographic characteristics, diagnosis, age at onset, disease duration, follow-up duration, clinical and laboratory variables, and outcome data were compiled. Gathered laboratory data were part of patients' usual medical care.

RESULTS: Thirty-four patients (females, 53%) with autoinflammatory diseases were included (mean age, 151 months. Mean disease duration was 118 months; mean age at onset was 32 months; consanguinity was present in 40%. Patients were diagnosed as follows: FMF, 50%; CRMO, 23.5%; CINCA, 8.8%; EOS, 8.8%; MWS, 6%; and PFAPA, 2.9%. The referral diagnosis was inaccurate in all patients except for FMF patients. Gene study was informative in 9 of 14 FMF patients who had molecular analyses. None of our cohort had amyloidosis. All CRMO patients had a favorable response to treatment except 1 patient, who had refractory, progressive disease. All patients with EOS had multiorgan involvement, including uveitis. All CINCA patients had a favorable response to anakinra.

CONCLUSION: Our report shows that autoinflammatory diseases other than FMF may be overlooked. Increased awareness among pediatricians about these conditions will help to provide better health care to patients in the form of early diagnosis and management.

Autoinflammatory diseases, also known as periodic fever syndromes, refer to a group of hereditary recurrent episodes of inflammation without evidence of the typical features of autoimmune diseases, such as high-titer autoantibodies or autoreactive T cells.[1,2] The concept of autoinflammatory diseases was introduced in 1990; these diseases primarily include familial Mediterranean fever (FMF), TNF receptor-associated periodic fever syndrome (TRAPS), hyperimmunoglobulinemia D syndrome (HIDS), and cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic infantile neurological cutaneous and articular syndrome (CINCA).[3] These conditions are characterized by recurrent attacks of fever, accompanied by other signs and symptoms of inflammation, particularly affecting the serous membranes, skin, eyes, bones, joints, gastrointestinal tract, and central nervous system. These symptoms sometimes overlap, obscuring diagnosis. Recently,

pyogenic arthritis syndrome, pyoderma gangrenosum and acne, Blau syndrome, early-onset sarcoidosis (EOS), and chronic recurrent multifocal osteomyelitis (CRMO) were added to the list of autoinflammatory diseases.[4]

Increased awareness of the distinguishing clinical features of autoinflammatory diseases and the use of specific functional tests when available are helpful. These factors have catalyzed early diagnosis and genotype-phenotype interaction and allowed dramatic breakthroughs in targeted biologic therapy.[1,5,6]

Both clinical and gene mutations of FMF have been reported in different Arab populations, particularly in East Mediterranean Arabs. The results of gene studies are similar to those reported in other studies among Sephardic Jews, Turks, and Armenians. On the other hand, data from Arab countries regarding other autoinflammatory diseases are scarce.[7-10] To the best of our knowledge, there are no published data from Saudi Arabia about autoinflammatory diseases, including FMF. In this study, we describe the clinical and laboratory features of autoinflammatory diseases in Saudi children.

PATIENTS AND METHODS

This study is a retrospective review of medical records of children who had autoinflammatory diseases and were evaluated at the Pediatric Rheumatology Clinic at King Faisal Specialist Hospital and Research Center, Riyadh, between January 1995 and January 2010. These included children with FMF, CRMO, EOS, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (PFAPA), CINCA, and MWS. Children with systemic-onset juvenile idiopathic arthritis (SOJIA) and Behçet disease were not included.

Data with regard to age, gender, origin, presenting symptoms, final diagnoses, laboratory studies, including imaging and genetic studies, diagnostic procedures, treatment, and outcome were reviewed. All of the laboratory data were part of the patients' usual medical care .

RESULTS

The study cohort consisted of 34 patients with different autoinflammatory diseases. They comprised 17 patients with FMF, 8 with CRMO, 3 with EOS, 3 with CINCA, 2 with MWS, and 1 with PFAPA. There were no patients with HIDS or TRAPS. **Table 1** shows the demographic features and the provincial distribution of the patients. There were 18 female and 16 male patients (female-to-male ratio, 1.1:1). Twenty-two (65%) patients were the product of first-degree consanguineous marriages. The mean age at onset was 32 months (range, 1-127 months), and the mean age at diagnosis was 56 months. The mean disease duration was 118 months (range, 10-250 months). Patients were from different geographical areas of Saudi Arabia, with the distribution as follows: 29.4% were from the central province, 17.6% from the northern province, 14.7% from the western province, and 38.2% from the southern province. Most of the FMF patients were referred with a correct diagnosis. However, the referral diagnosis was inaccurate in patients with other conditions.

Table 2 shows the frequency of clinical features. Recurrent fever (94%) was the most frequent symptom, followed by musculoskeletal pain (76%). Gastrointestinal tract involvement was not uncommon: 53% had abdominal pain, 50% had vomiting, and 47% had diarrhea. Fourteen (41%) patients had nonspecific skin rash. Neurological symptoms as manifested by isolated headache were noted in 26% of the patients, but there were no other neurological findings. Seventeen patients were from 14 unrelated families, but there were 4 affected siblings from the same family. Fever was the presenting feature in all FMF patients, and febrile episodes ranged from 3 to 5 days; 76% of these patients had associated chills, while skin rashes were present in only 18% of patients. Arthralgia was common (88%), but definite arthritis was noted in only 12% of patients. Abdominal pain and diarrhea were common among FMF patients (88% and 82%, respectively). One patient with FMF had an unusual musculoskeletal finding; he was shown to have bilateral sacroiliitis, as confirmed by magnetic resonance imaging (MRI). Acute phase reactants, namely, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were elevated during symptomatic episodes in 35% of FMF patients. Gene studies were informative in 9 of 14 FMF patients who had molecular analyses. All FMF patients were treated with colchicine. Most of these patients showed a good response to colchicine, with complete remission after treatment. However, 4 patients showed only a partial response to colchicine and a nonsteroidal anti-inflammatory drug (NSAID); therefore, they were treated with short courses of prednisone.

All 3 CINCA patients were males, with a mean age of 132 months (range, 81-171 months). The mean age at onset was 2.3 months (range, 1-4 months), and the mean disease duration was 130 months (range, 77-170 months). The first clinical manifestations for these patients were skin rash and fever; all 3 patients had chronic headache and bony overgrowth, mainly in the patella. Elevated levels of ESR and CRP with leukocytosis were also seen. All 3 patients had conjunctivitis, and 1 patient had squint, with normal funduscopy results. This pa-

Table 1. Demographic features and the province distribution of the patients.

	Total number of patients	Number of Patients					
		FMF	CINCA	CRMO	EOS	MWS	PFAPA
Gender							
Male	16	12	3	1	0	0	0
Female	18	5	0	7	3	2	1
Origin							
Central	10	4	1	1	1		
North	6	5	0	0	1		
West	5	3	1	1	0		
South	13	5	1	6	1		
Consanguinity	22	12	2	6	2	0	1
Age range (months)	63-269	63-260	81-171	79-204	79-140	84-127	66
Age range at onset (months)	1-127	8-127	1-4	3-78	18-74	9-48	13
Disease duration, range (months)	10-250	51-250	77-170	24-155	60-66	75-79	53

CINCA: chronic infantile neurologic cutaneous and articular syndrome, CRMO: chronic recurrent multifocal osteomyelitis, EOS: early-onset sarcoidosis, FMF: familial Mediterranean fever, MWS: Muckle-Wells syndrome, PFAPA: periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome

Table 2. Frequency of the clinical and laboratory findings.

	Number of patients						
	Total (n=34)	FMF (n=17)	CINCA (n=3)	CRMO (n=8)	EOS (n=3)	MWS (n=2)	PFAPA (n=1)
Fever	31	17	3	5	3	2	1
Rash	12	3	3	0	3	2	1
Arthralgia	26	15	3	4	1	2	1
Arthritis	7	2	3	2	0	0	0
Bone pain	6	4	1	0	0	1	0
Uveitis	3	0	0	0	3	0	0
Vomiting	17	13	0	0	1	2	1
Diarrhea	16	14	0	0	1	0	1
Abdominal pain	18	15	0	0	0	2	1
Headache	9	3	3	0	0	2	1
Leukocytosis	9	5	3	0	0	0	1
High ESR	20	6	3	6	3	1	1
High CRP	17	5	3	4	3	1	1
High ACE	3	ND	ND	ND	3	ND	ND
High ANA	3	1	0	0	0	2	0

ACE: angiotensin-converting enzyme, ANA: antinuclear antibody, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ND: not done

Table 3. Main features useful in distinguishing among the autoinflammatory diseases.

Disease	Duration of fever	Clinical features	Mode of inheritance	Gene
FMF	1-3 days	Peritonitis, pleuritis, erysipelas-like rash, arthritis	AR	MEFV
MWS	1-2 days	Urticaria, progressive sensorineural hearing loss	AD	CIAS1
CINCA	Continuous	Developmental delay, aseptic meningitis, epiphyseal overgrowth, facial dysmorphic appearance	AD	CIAS1
EOS	Variable	Noncaseating granulomatous rash, arthritis, uveitis,	AD	NOD2
CRMO	Variable	≥2 Typical bony lesions, no isolated pathogens	AR	LPIN2
TRAPS	2-14 days	Abdominal/chest pain, migrant skin lesions, myalgia, arthralgia, periorbital edema	AD	TNF RSF1A

AD: autosomal dominant, AR: autosomal recessive, TRAPS: TNF receptor-associated periodic fever syndrome

tient also had features of attention-deficit disorder and delayed speech; brain MRI revealed nonspecific white matter changes. The other 2 patients had normal neurological findings, as well as normal brain neuroimaging studies. Initially, the CINCA patients were treated with NSAIDs, prednisone, and methotrexate; subsequently, two patients were administered etanercept, with poor response. However, anakinra induced a dramatic response in the form of resolution of the clinical features and normalization of the clinical and laboratory results.

Of the 8 CRMO patients, 7 (88%) patients were female. Age ranged from 79 to 204 months, and age at onset ranged from 3 to 78 months; fever and musculoskeletal pain were the common features. Recurrent fever was present in 63% of these patients; all patients had bone pain, with arthralgia and arthritis in 50% and 25% of patients, respectively. The sites of osteomyelitis were femur, tibia, ankle, navicular bone, scapula, ribs, and vertebrae. One patient had severe disease, and she was disabled and wheelchair dependent. She had multiple bony involvements, including cervical, thoracic, and lumbar vertebrae, right hip, iliac bones, scapulae, and ribs. She was found to have sickle cell trait. Six of CRMO patients had elevated ESR, whereas CRP was elevated in four patients; none of the patients had leukocytosis. All CRMO patients were treated with NSAIDs, and five of them required short courses of prednisone. Three patients were treated with pamidronate. The disabled patient showed good response and started to mobilize.

All three EOS patients were female. The mean age at onset was 46 months, and the mean disease duration was 101 months. All patients had skin rash, hepatosplenomegaly, and uveitis. Vomiting and abdominal pain were present in one patient, and the other patients had arthralgia. All had elevated levels of ESR, CRP, and angiotensin-converting enzyme (ACE), and the diagnosis was confirmed by tissue biopsy (one patient had splenic biopsy and two patients had skin biopsy). Histopathologic findings showed noncaseating granuloma; cultures were negative for acid-fast bacilli and fungi. All three patients were treated with NSAIDs, prednisone, and methotrexate. Two patients had poor response and required infliximab infusion.

Two sisters presented with clinical features highly suggestive of MWS; their age at onset was 9 months and 48 months, respectively. They presented with recurrent fever, abdominal pain, urticarial skin rash, arthralgia, and headache; one of them had sensorineural deafness. The results of laboratory tests were benign; they had normal CBC and CRP, occasionally high ESR, and a normal serum immunoglobulin D level. They had positive antinuclear antibody (1:320). However, extractable nuclear antigens were negative. Both patients failed NSAID and colchicine therapy; recently, they were treated with anakinra, with partial response.

Only one girl (66 months old) had features consistent with PFAPA. Her disease started at the age of 13 months. She had frequent attacks of fever with chills, pharyngitis, skin rash, arthralgia, vomiting, diarrhea, and abdominal pain. Her laboratory results showed elevated ESR and CRP, as well as leukocytosis. She was treated with colchicine and NSAIDs, with partial response. She showed good response to prednisone.

DISCUSSION

Autoinflammatory diseases are a group of disorders with shared classic clinical features in the form of recurrent acute short-lived febrile attacks with variable periods of remission. Other common clinical features are recurrent and usually short attacks of polyserositis, synovitis, and various skin eruptions.[1,2]

To date, many gene mutations have been recognized in the pathogenesis of various autoinflammatory diseases, for example, Mediterranean fever (MEFV) for FMF, cold-induced autoinflammatory syndrome 1 (CIAS1) for CAPS, and nucleotide-binding oligomerization domain 2 gene (NOD2) for EOS.[6,11]

Table 3 shows the main features useful in distinguishing these diseases. In children who are suspected of having an autoinflammatory disease, an accurate clinical history and a physical examination remain the first diagnostic tools. To date, genetic testing has not replaced clinical diagnosis; it should be performed only in highly suggestive cases. Furthermore, only 50% of affected patients have positive genetic tests, suggesting that many genetic loci are still unknown.[11]

This study analyzed the clinical and laboratory features of 34 patients from unrelated families, referred from different provinces of Saudi Arabia and evaluated at the largest tertiary health care center in the country. These patients' diagnoses included the following: FMF, CRMO, EOS, PFAPA, CINCA, and MWS. As expected, fever was the most frequent finding, followed by musculoskeletal symptom; only 14 (41%) patients had cutaneous findings. There was a delay in establishing the accurate diagnosis in patients with FMF; only 10 of 17 had the correct diagnosis before referral to our center. The main reason for referral of patients with established FMF diagnosis was to conduct the gene study.

Although this study may not be an inclusive one, it includes some case series of rare diseases. It is clear that our study provides no data on incidence. We believe that our study excluded a number of patients with FMF, since these patients are usually followed up and managed by pediatricians and our clinic was perhaps only seeing patients with unclear diagnosis or those who needed further confirmatory genetic tests. One patient with FMF was referred to us and followed as a case of SO-JIA and treated unnecessarily with steroid and methotrexate, with the diagnosis of FMF suspected based on history and confirmed by molecular genetic test. On the other hand, patients with other autoinflammatory diseases were referred with inaccurate diagnosis, such as JIA, infection, malignancy, or immunodeficiency. These patients were referred from different provinces of Saudi Arabia, indicating that our cohort is likely representative of the whole country. As expected, FMF was the most frequent autoinflammatory disease (48.5%) among our cohort; all FMF patients were Arabs. Some patients were from central and south provinces, which are geographically far from the Mediterranean region. FMF particularly affects non-Ashkenazi Jews, Armenians, Turks, and East Mediterranean Arabs, but other Arabs may be affected as well. Interestingly, FMF has been reported in Japan and the Far East.[12] Our patients with FMF had clinical and genetic findings similar to those reported in East Mediterranean Arabs and other populations.[7,9]

Other autoinflammatory diseases may overlap in their clinical expression with more common entities like infection and JIA. However, there are specific clinical findings, and a high level of suspension is needed in such cases.[4,13] Regarding CINCA, age at onset is probably different; as it was found to start in the neonatal period, unlike other autoinflammatory diseases or SO-JIA. Unfortunately, none of the usual laboratory results are diagnostic of autoinflammatory disease. However, the presence of noncaseating granuloma and high ACE level is highly suggestive of EOS. It is important to emphasize that CRMO has clinical and imaging findings similar to those of bacterial osteomyelitis; to obtain a diagnosis, the treating physician needs to exclude mimicking conditions.[14]

Autoinflammatory diseases are chronic diseases that may be complicated by serious problems; therefore, early diagnosis and initiation of proper therapy are necessary to minimize these complications and improve the patient's quality of life. Untreated FMF patients may develop amyloidosis. All of our patients were treated with colchicine; fortunately, none of them had amyloidosis.[15] The past decade has shown tremendous growth in understanding the molecular basis of autoinflammatory diseases, especially regarding cryopyrinopathies, suggesting improvements in treatment of these conditions. Currently, an interleukin-1 blocker (anakinra) is considered to be a new effective therapy for CINCA patients. Our CINCA patients had favorable response to this medication. It suppresses disease progression and ameliorates the general condition of patients.[16]

The paucity of autoinflammatory diseases reported other than FMF may not indicate a low frequency of these among Saudi children; rather, it may indicate the underlying difficulties in establishing or confirming the diagnosis of such diseases. This report is intended to increase the awareness among pediatricians about these conditions, in the hope that it will help to provide better health care to these patients in the form of early diagnosis and management.

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