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Clinical Observations

Familial Mediterranean fever—renal involvement by diseases other than amyloid

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Abstract

Background. In patients with familial Mediterranean fever (FMF) renal involvement is usually in the form of AA amyloidosis. There is increasing evidence that renal involvement may be due to diseases other than amyloid as well.

Methods. Amongst 302 children with FMF we observed and followed 28 with typical clinical and laboratory features of vasculitis. The diagnosis of FMF was established according to the Tel Hashomer criteria.

Results. Polyarteritis nodosa, protracted febrile attacks and Henoch–Schönlein purpura were diagnosed in 4, 13, and 11 patients, respectively. The presentation was often difficult to distinguish from FMF attacks, but protracted febrile attacks lasting several weeks, hypertension, thrombocytosis, and dramatic responses to corticosteroid therapy that were observed in many cases were different from what is observed in classical FMF.

Conclusions. We suggest that FMF, perhaps as a consequence of impaired control of inflammatory responses, predisposes to vasculitis with renal involvement.

Key words: familial Mediterranean fever, vasculitis, children, glomerulonephritis

Introduction

Familial Mediterranean fever (FMF) is a recessively inherited disorder of inflammation that commonly affects Turks, Jews, Armenians, and Arabs. The classical clinical findings of FMF consist of recurrent self-limited attacks of fever accompanied by peritonitis, arthritis, and erysipelas-like erythema. The FMF gene (MEFV) and four missense mutations were identified recently by two independent groups [1,2]. The discovery of this novel gene will have important clinical and pathogenetic implications. The occurrence of vasculitic conditions such as polyarteritis nodosa (PAN) and Henoch–Schönlein purpura (HSP) with FMF have been described in anecdotal reports [3–5]. Based on a large cohort of children with FMF we tried (i) to provide a crude estimate of the prevalence of vasculitis and (ii) to characterize its clinical features in patients with FMF.

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Materials and methods

This study was performed in two hospitals located in Ankara. It included 28 FMF patients who were investigated and followed at the hospital. The diagnosis of vasculitis was based on typical clinical and laboratory features. In 13 patients the diagnosis was confirmed by the results of the biopsies of the affected skin and in three by the demonstration of microaneurysms on renal angiography. The diagnosis of FMF was established according to the Tel Hashomer criteria [6]. Henoch–Schönlein purpura and PAN were diagnosed according to previously described criteria [7,8].

Results

Twenty-eight (9%) of the 302 FMF children seen over the 10-year period from January 1988 to December 1997 were given the diagnosis of vasculitis. Polyarteritis nodosa, protracted febrile attacks and HSP were diagnosed in four (1.32%), 13 (4.3%) and 11 (3.6%), respectively. Over the same 10-year period the frequency of PAN and HSP amongst the non-FMF patients observed in two hospitals in which the study was performed were 4/100 000 and 50/100 000, respectively. Table 1 shows the clinical and laboratory features of the study group. In 24 patients who had the history of typical attacks existing for 1–14 years, the diagnosis of FMF could be established only after the diagnosis of vasculitis had been made. In four children FMF was diagnosed 2–5 years before vasculitis developed. In two of the four children vasculitis developed while they were taking colchicine therapy. Sixty-five per cent of the study group had a positive

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Table 1. Clinical and laboratory findings of the patients

	Polyarteritis nodosa	Protracted febrile attack	Henoch–Schönlein purpura
No of patients	4	13	11
Male/Female	3/1	4/9	6/5
Age at onset of vasculitis	11.75 ± 1.5	8.6 ± 2.3	10.6 ± 2.3
Fever	4/4 (100%)	13/13 (100%)	6/11 (55%)
Fatigue-anorexia	4/4 (100%)	13/13 (100%)	7/11 (64%)
Skin eruptions	3/4 (75%)	11/13 (85%)	11/11 (100%)
Abdominal pain	3/4 (75%)	9/13 (69%)	11/11 (100%)
Hypertension	3/4 (75%)	8/13 (62%)	0/11 (0%)
Myalgia	2/4 (50%)	12/13 (92%)	3/11 (27%)
Arthritis	1/4 (25%)	7/13 (54%)	8/11 (73%)
Hepato-splenomegaly	2/4 (50%)	9/13 (69%)	3/11 (27%)
WBC (mm^3)	30 450 ± 7726	16 869 ± 6968	15 120 ± 10 274
Haemoglobin (g/dl)	9.9 ± 3.5	9.7 ± 1.5	11 ± 1.9
Platelet count (mm^3)	588 500 ± 35 874	537 000 ± 156 823	466 000 ± 255 325
ESR (mm/h)	107 ± 22	97 ± 25	84 ± 41
Haematuria	0/4 (0%)	3/13 (23%)	3/11 (27%)
Proteinuria	0/4 (0%)	2/13 (15%)	2/11 (18%)
Hypocomplementemia	1/4 (25%)	0/13 (0%)	0/6 (0%)
Occult blood in stool	1/2 (50%)	2/13 (15%)	0/5 (0%)
Electromyography	1 myopathy	7 myopathy 1 mononeuritis multiplex	1 myopathy
Aneurysms on angiography	3/4 (75%)	0/9 (0%)	—

Table 2. Histopathologic findings of the patients

		Polyarteritis nodosa	No.	Protracted febrile attack	No.	Henoch–Schönlein purpura	No.
Skin biopsy	Light microscopy	Perivascular MNC[a] infiltration	1	Perivascular MNC[a] infiltration	4	LCV[a]	4
				Normal	4	Perivascular MNC[a] infiltration	4
	Immune fluoresceint microscopy					C3	3
				IgM	2	Fibrinogen	2
		Negative	1	Fibrinogen	1	IgM	2
				C3	1	IgA	1
						Negative	1
Renal biopsy	Light microscopy	—		FPGN[a]	1	MPGN[a]	1
	Immune fluoresceint microscopy	—		C3	1	IgM	1
				IgM	1	C3	1
				IgA	1		
Muscle biopsy	Light microscopy	Normal	1	Normal	6	Perivascular MNC infiltration	1
	Immune fluoresceint microscopy	Negative	1	IgM	1	IgM	1
				Fibrinogen	1		

[a]MNC: mononuclear cell; MPGN: membranoproliferative glomerulonephritis; LCV: leukocytoclastic vasculitis; FPGN: focal proliferative glomerulonephritis.

family history of FMF. A child who was diagnosed as PAN and another with protracted febrile myalgia were siblings. The diagnosis of HSP without FMF was described in the brother of another patient. Two patients had a history of HSP and another protracted febrile myalgia in their siblings with FMF. Three relatives from two patients had the diagnosis of Behçet's disease.

(i) Polyarteritis nodosa

The clinical and laboratory features of four patients were consistent with the diagnosis of PAN. All of them had constitutional symptoms such as fatigue, anorexia, and weight loss. Microaneurysims on angiography were found in three children (Figure 1). One of them also had acute scrotal swelling with severe tenderness and pain. Testis biopsy revealed polyarteritis with

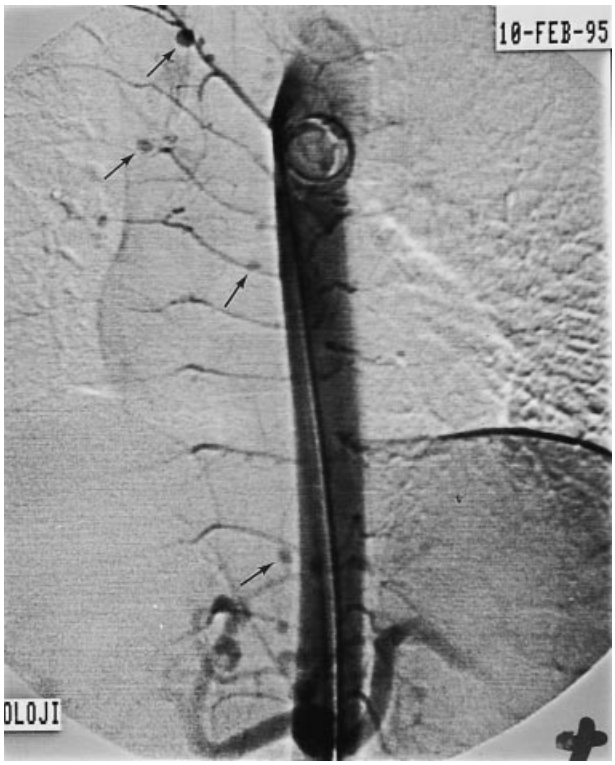


Fig. 1. Microaneurysms of the intercostal arteries on angiography.

massive periarterial neutrophilic infiltration and fibrinoid necrosis of the arterial wall. The fourth patient had a history of abdominal surgery because of an intra-abdominal haematoma 2 weeks before admission. Upon examination, he was a thin, pale and wasted boy. He had fever and severe abdominal pain. Abdominal ultrasonography revealed multiple nodular heterogenous hypoechoic lesions of 9–25 mm diameters in the lateral segment of the left lobe of liver (Figure 2). Hepatitis B serology was negative in all the

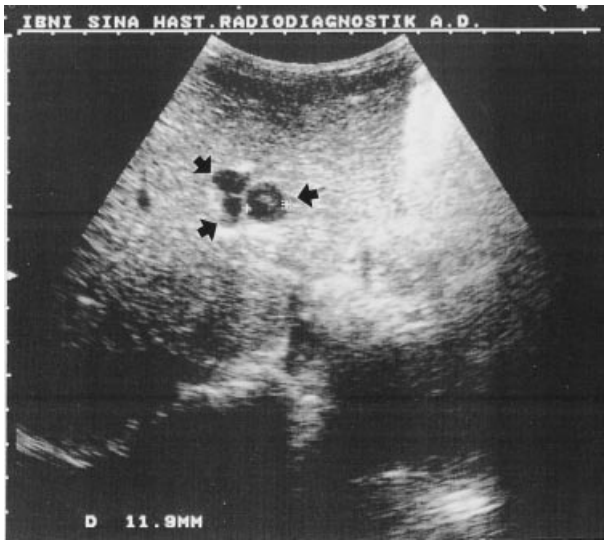


Fig. 2. Multiple nodular heterogenous hypoechoic lesions in the liver by abdominal ultrasonography.

patients who had the diagnosis of PAN. Corticosteroid therapy was commenced to these four patients. A dramatic response was observed in three of them within several days. However, in one patient no improvement was achieved until cyclophosphamide was added to the treatment.

(ii) Protracted febrile attacks

The second group consisted of 13 patients who had been suffering from protracted febrile attacks persisting at least 4 weeks. All of them had constitutional symptoms similar to the patients with PAN. However, neither biopsies of the involved area nor angiographic findings supported the diagnosis of PAN. Twelve had severe myalgia especially of the proximal muscles of the extremities. The findings of these 12 patients were consistent with the diagnosis of protracted febrile myalgia that was reported as an uncommon dramatic manifestation of FMF [9]. Protracted arthralgia and arthritis were the major complaints of the last patient, while myalgia was not a predominant symptom. Three patients had renal involvement and kidney biopsy revealed focal proliferative glomerulonephritis in one of them. Ten patients in this group were treated with corticosteroids. A dramatic response was achieved with the resolution of the symptoms in most of them. Three received only colchicine treatment. Gradual improvement of the symptoms was observed within a week. However, one of these patients had a similar episode after 2 years on colchicine treatment. Increasing doses of colchicine failed to bring any improvement and no remission was achieved until steroids were given.

(iii) Henoch–Schönlein purpura

Eleven patients were diagnosed as HSP. In six of them several attacks of purpura, mainly in the lower extremities, were described before the diagnosis of HSP. Three children whose skin biopsies revealed leukocytoclastic vasculitis had also severe myalgia persisting for several weeks. Muscle biopsy was consistent with vasculitis in one of these patients. Renal biopsy revealed membranoproliferative glomerulonephritis in another child who had microscopic haematuria and proteinuria. Spontaneous remission occurred in eight patients. Three patients were treated with corticosteroids. All symptoms disappeared within several days.

We categorized our patients into three groups based on their diagnostic features (Table 1). However, most of the patients had similar symptoms and signs. The total duration of the disease exceeded 4 weeks in all except four patients who had HSP. The main complaints were fatigue and anorexia. These constitutional symptoms occurred in more than 80% of the patients. Skin eruptions that were observed in all except three of our group were one of the most frequent manifestations that occurred in the lower extremities between the knee and the ankle, over the ankle joint or on the dorsum of the foot. These were petechial rashes on the involved erythematous swollen and tender area that

were noted in nine patients, lasted in 1 or 2 days (Figure 3). In addition, livedo reticularis, malar rash and maculopapular rash were observed in two and urticaria accompanied by scalp and facial oedema was observed in one of the patients (Figure 4). Severe myalgia, arthritis, and hypertension were noted in 17 (61%), 16 (57%) and 11 (39%) patients. Severe myalgia was mainly localized in the proximal muscles of the upper and lower extremities. Muscle enzyme activities were normal. Electromyography documented myopathy in nine patients and mononeuritis multiplex in one.



Fig. 3. Petechial rash on the involved erythematous and swollen area.



Fig. 4. Facial and scalp oedema of the patient.

Muscle biopsies of the seven patients who had severe myalgia were normal, but one who had the clinical diagnosis of HSP with severe myalgia had non-specific vasculitis on light microscopy of the involved muscles.

Conclusion

The occurrence of a variety of vasculitic syndromes in patients with FMF has been described before [10]. The coexistence of HSP and PAN with FMF has also been reported before and it was proposed that these conditions occur more frequently in FMF than in the general population [3–5]. The clinical and laboratory features of our patients suggested a broad spectrum of vasculitic syndromes. In some of the children the presentations resemble PAN and in some HSP, with a change in the usual pattern of FMF attack. Almost all of our patients, except some with HSP, had a protracted attack lasting several weeks—in contrast to the classical FMF attack that lasts less than a week. Hypertension and thrombocytosis, which are almost never noted in a classical FMF attack, were found in 39% and 75% of our patients, respectively. Finally, a dramatic response was achieved in almost all of our patients who received corticosteroid therapy. All of these findings indicate that the presentation of a vasculitic attack is different from that of a typical FMF attack.

The gene responsible for FMF has been cloned recently. The gene product called pyrin/marenostrin is a nuclear transcription factor that controls the inflammatory response by regulating the expression of some target genes that are involved in the suppression of inflammation [1,2]. In addition, circulating immune complexes, complement consumption and increase in the level of immune globulins were described in FMF patients [11–13]. As the gene product was thought to be responsible for the inhibition of inflammation, it was suggested that the FMF-associated mutations and resultant structural changes of the protein prevent the normal pyrin/marenostrin-mediated negative feedback mechanism and trigger inflammation [1,2]. C5a inhibitor, which was described as a deficient protein in FMF patients, probably acts as a part of this complex anti-inflammatory mechanism [14].

The pathogenesis of vasculitis in patients with FMF is unknown. An immune complex mechanism was proposed [3]. The presence of immunoglobulins and C3 in the biopsy specimens of our patients supports this hypothesis. The coexistence of the findings of our patients seems to be too frequent to be explained by chance. It was suggested that FMF patients might have an unusual response to some infections as a result of an imbalance of immune regulation [4,15].

We could not observe a significant difference in the frequency of mutations of the FMF gene between vasculitic and non-vasculitic FMF patients (unpublished data). This finding indicates that a genetic basis of vasculitis if it exists, is not related to known FMF mutations. It is very interesting to note that more than one member developed vasculitis in some families in

our series. A review of the world literature reveals that one of the largest pediatric PAN series was reported from Turkey [16]. It seems wise to consider a role for both genetic and environmental factors in the genesis of vasculitides in the patients with FMF.

In conclusion, in the view of the association and clinical similarities between vasculitis and FMF we propose that the frequent occurrence of vasculitis with renal involvement in the patients with FMF is the result of an exaggerated uncontrolled inflammatory response in FMF.

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