Egyptian Rheumatology and Rehabilitation

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Neurological manifestations among Egyptian children with familial Mediterranean fever

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Abstract

Background Familial Mediterranean fever (FMF) is an auto-inflammatory periodic disorder resulting from mutations in the Mediterranean fever gene. Although it is considered a polyserositis disease, neurological-associated symptoms were also reported among different populations.

Aim of the work To detect the frequency of neurological manifestations among Egyptian children with FMF and to investigate its association with various disease characteristics and various FMF gene mutations.

Patients and methods This is an analytical cross-sectional study that enrolled 300 FMF children. Neurological manifestations such as headache, paresthesia, convulsions, tremors, breath-holding attacks, and syncope were reported. The dose, duration, and compliance with colchicine and the international severity scoring system for FMF (ISSF) were recorded. Serum amyloid A and gene mutations were recorded from patients' files.

Results The mean age of the patients was 10.35 ± 2.89 years; 158 (52.7%) were females, and 142 (47.3%) were males (F:M, 1.1:1), age at onset 4.67 ± 2.35 years and disease duration 3.28 ± 1.31 years. Genetic testing revealed positive MEFV gene mutation in 89.3%. Serum amyloid A was elevated in 33.7%. All patients were treated with colchicine, and 81.3% were compliant. Neurological manifestations were detected in 160 (53.3%) patients. Headache was the most common symptom in 136 (45.3%), followed by paraesthesia in 76 (25.3%). Epilepsy was present in 7 (2.3%) cases. Headaches were most frequent among patients with compound heterozygous mutation, severe ISSF scores, and poor compliance with colchicine.

Conclusion Egyptian children with FMF present with various neurological manifestations. Headache and paresthesia were the most frequent, especially with the compound heterozygous mutations, severe ISSF score, and among colchicine non-compliant patients. Rheumatologists and neurologists should be aware of these manifestations and address the importance of disease control and adherence to colchicine to avoid or decrease these manifestations. Persistent unexplained headache or other neurological manifestations, in the presence of other symptoms suggestive of FMF or high serum amyloid A, should raise suspicion of FMF, and genetic testing should be requested. A multidisciplinary approach must be considered when managing these children.

Keywords Parathesia, Epilepsy, ISSF, Colchicine compliance

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Background

Familial Mediterranean fever (FMF) is the most common hereditary auto-inflammatory disease. It is an autosomal recessive disorder, primarily occurring in populations from the Mediterranean region, namely Turks, Arabs, and Armenians [1]. It is characterized by short-lived

recurrent episodes of fever, peritonitis, pleuritis, arthritis, and rash [2]. The first attacks typically begin during childhood and last 12–72 h [3]. The responsible gene of FMF is the mutated pyrin/marenostrin, a protein composed of 781 amino acids that can regulate interleukin 1β (IL-1β) production. Pyrin interacts with caspase-1 and the nucleotide-binding domain leucine-rich repeat/pyrin domain containing 3 (NLRP3), which are fundamental parts of the inflammasome complex [4]. More than 300 mutation variants are located on the *MEFV* gene [5]. Amyloidosis can manifest in young children and during the early stages of the disease, indicating that the disease's duration is not the only factor contributing to the development of this condition [6]. Previous research detected a broad spectrum and high prevalence of neurological manifestations in adult patients with auto-inflammatory diseases predominantly caused by various low-penetrance mutations in the *NLRP3-*, *MEFV-*, or *TNFRSF1A* gene [7]. Although FMF is a polyserositis disease, there is also central nervous system (CNS) involvement and many neurological-associated symptoms [8]. Some neurological disorders that might be relevant to FMF have been attributed to cerebral venous sinus thrombosis, pseudotumor cerebri, optic neuritis, and CNS complications of systemic vasculitis (Henoch–Schonlein purpura, polyarteritis nodosa, Behcet's disease) [9]. Demyelinating lesions and multiple sclerosis were reported frequently among FMF patients [10]. Cerebral vasculitis and hypercoagulable state secondary to amyloidosis have also been reported in patients with FMF [11]. Some case reports have revealed the coexistence of familial Mediterranean fever and posterior reversible leukoencephalopathy [8].

Interestingly, recurrent isolated transverse myelitis following FMF attacks was reported in adult FMF patients. It improved with treatment with rituximab [12]. The pathogenesis of CNS involvement in FMF is unclear and is a subject of debate [8]. It was suggested that producing IL-1β and other pro-inflammatory cytokines, with a recognized role in the pathogenesis of demyelinating disorders, could explain FMF-associated demyelination [13]. Recent studies detected an increased prevalence of neurodevelopmental disorders among FMF children, mainly attention deficit hyperactivity disorder (ADHD) [14]. Witt et al. detected that the signs and symptoms of autonomic dysfunction are more prevalent in FMF patients than in age- and gender-matched healthy controls [15].

Colchicine is the currently recommended medication for FMF. Its goal is to prevent FMF attacks and to reduce acute phase reactants, such as serum amyloid A [16]. Compliance with therapy is essential for controlling and managing the disease [17]. Even though FMF typically manifests as intermittent acute attacks, a proportion of patients experience complications, adherence to therapy, and early diagnosis are critical components of patients' health [18].

This study aimed to detect the frequency of neurological manifestations among Egyptian children with FMF and to study its relation to different disease characteristics, compliance with treatment, and types of genetic mutations.

Patients and methods

This study included 300 children diagnosed with FMF, according to the Yalçinkaya et al. [19] criteria, and was followed up in the Pediatric Rheumatology Outpatient Clinic from April 2021 to October 2021. The Faculty of Medicine Ethical Committee approved the study (MS 223–2021).

All patients were under the age of 16 years, and they did not have any concomitant rheumatological disease. The study objectives, steps, and potential benefits were discussed with caregivers of all study participants or their children if older than 12 years. All participants were enrolled after receiving their caregivers' informed written consent.

Full history taking includes demographic data, age of onset of FMF, age at diagnosis, disease duration, FMF features during illness course, and neurological manifestations such as headache, paresthesia, convulsions, tremors, breath-holding attacks, and syncope. Also, dose and compliance with colchicine and the international severity scoring system for FMF (ISSF) [20] were recorded. MEFV gene mutations and the last result of serum amyloid A were collected from patients' files.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences software (SPSS) version 21. The data were presented as numbers, percentages, or mean, standard deviations, and ranges**.** Quantitative variables were compared using the non-parametric Mann–Whitney test. Correlations between quantitative variables were done using the Spearman correlation coefficient. Parametric and non-parametric statistical tests and correlation and regression analyses were done for data accordingly. Significance was considered if the *p*-value was equal to or below 0.05.

Results

The 300 FMF children were 158 (52.7%) females and 142 (47.3%) males (F:M, 1.1:1) with a mean age of 10.35 ± 2.89 years. The characteristics of the patients are presented in Table 1. Positive family history of FMF was reported by 124 (41.3%) patients and 135 (45%) had parental consanguinity. Abdominal pain was the most frequent manifestation among our patients in 289 (96.3)%, followed by arthralgia 258 (86%), fever 231 (77%), chest pain 74

Table 1 Characteristics of the familial Mediterranean fever (FMF) children

Parameter mean ± SD (range) or no. (%)	FMF patients ($n=300$)
Age (years)	10.35 ± 2.89 (3–15)
Female:male	158:142 (1.1:1)
Age at onset (years)	4.67 ± 2.35 (0.5–10)
Age at diagnosis (years)	7.08 ± 2.72 (1–14)
Disease duration (years)	3.28 ± 1.31 (1–10)
Family history of FMF	124 (41.3)
Positive consanguinity	135 (45)
FMF manifestations	
Abdominal pain	289 (96.3)
Fever	231 (77)
Arthralgia	258 (86)
Chest pain	74 (24.7)
Scrotal affection (males $n=142$)	17 (12)
Arthritis	4 (1.3)
Rash	3 (1)
Vasculitis	2 (0.7)
Neurological manifestations	
Headache	136 (45.3)
Paresthesia	76 (25.3)
Breath-holding attacks	34 (11.3)
Tremors	27 (9)
Febrile convulsions	17 (5.7)
Syncope	15 (5)
Epilepsy	7 (2.3)
MEFV gene mutation	
Homozygous	28 (9.3)
Heterozygous	217 (72.3)
Compound heterozygous	23 (7.7)
No mutation	32 (10.7)
Positive CRP	49 (16.3)
Serum amyloid A (mg/L)	13.35 ± 15.10 (0.1–180)
Elevated	101 (33.7)
ISSF	3.3 ± 0.8
Mild	38 (12.7)
Intermediate	257 (85.7)
Severe	5 (1.7)
Colchicine dose (mg/day)	0.99 ± 0.33 (0.5–2)
Compliance	244 (81.3)

FMF familial Mediterranean fever, *CRP* C-reactive protein, *ISSF* international severity scoring system for FMF

(24.7%), arthritis 4 (1.l3%), rash 3 (1%), and vasculitis 2(0.7%). A history of scrotal affection was detected in 17 (12%) of male patients included in this study. Genetic testing revealed positive MEFV gene mutation in 89.3%. The heterozygous mutation was the most frequent mutation among our study group in 72.3%, followed by the homozygous mutation in 9.3% and the compound heterozygous mutation in 7.7%. Serum amyloid A was elevated in 33.7%. All patients were treated with colchicine, and 81.3% were compliant. As regards the history of neurological symptoms, headache was reported in 45.3%, followed by paraesthesia, breath-holding attacks, tremors, convulsions, and syncope with the following frequencies respectively 25.3%, 11.3%, 9%, 5.7%, and 5%. Syncope in all patients was vasovagal. During follow-up, epilepsy was diagnosed in 7 patients, while in the remaining FMF patients who developed convulsions, it was febrile convulsions.

The relationship between different neurological manifestations and MEFV genotype, ISSF score, and compliance with colchicine is shown in Tables 2 and 3. Headaches were frequently observed among patients with compound heterozygous mutation in 65.2%. All patients with severe ISSF scores had headache; 42 (75%) of those who were not compliant with colchicine had headache. Paresthesia and tremors were present in 80% of patients with severe ISSF scores. Most epileptic patients had a heterozygous mutation (57.1%), while 1 had no MEFV gene mutation. Regarding compliance with colchicine and disease severity score, only one patient was not compliant with colchicine and had a severe ISSF score.

No significant correlation existed between elevated serum amyloid A and different neurological manifestations.

Discussion

FMF is the prototypal auto-inflammatory disease characterized by recurrent bursts of systemic inflammation [21]. Although it is a systemic disease, neurological manifestations might exist [22]. Different neurological signs and symptoms have been reported in children with FMF in different case series [23]. Commonly reported neurological manifestations among FMF patients include myalgia and recurrent or chronic aseptic meningitis that responds to colchicine [8]. Also, AA amyloidosis is a long-term complication and may result in peripheral neuropathy [24].

Neurological symptoms were present in 53.3% of our FMF patients, and this is more than the results obtained by Bektas et al., in which neurological manifestations were detected in 23.5% [23], and Brio et al. who reported the prevalence of neurological symptoms among pediatric cases with FMF as 12.8% [25]. Furthermore, in a Turkish study, neurological symptoms were present in 21.5% of cases [26]. Headache was the most common neurological symptom among the current patients in 50%; similar results were obtained by Salehzadeh et al. in which headache was found in 47.6% of cases [27]. The study conducted by Baktes et al. detected headache in

Table 2 Neurological manifestations of familial Mediterranean fever (FMF) children in relation to genotype

Manifestation *n* (%)	Genotype in FMF patients (*n* = 300)				*p*
	Homozygous (*n* = 28)	Heterozygous (*n* = 217)	Compound (*n* = 23)	No mutation (*n* = 32)	
Headache	8 (19.3)	93 (42.9)	15 (65.2)	20 (62.5)	**0.03***
Paresthesia	4 (14.3)	58 (26.7)	8 (34.8)	6 (18.8)	0.28
Convulsions					
Febrile	1 (3.6)	13 (7.8)	1 (13)	2 (9.3)	0.49
Epilepsy	0(0)	4(1.8)	2(8.7)	1(3.1)	
Tremors	2 (7.1)	23 (10.6)	0(0)	2 (6.3)	0.34
Breath holding	3 (10.7)	20 (9.2)	3 (13)	3 (9.3)	0.07
Syncope	0 (0)	11 (5.1)	3(1.3)	1(3.1)	0.16

FMF familial Mediterranean fever. Pearson's correlation coefficient, bold values are significant at $p \leq 0.05$

Table 3 Neurological manifestations of familial Mediterranean fever (FMF) children with international severity scoring system for FMF (ISSF) and compliance to colchicine

Manifestation *n* (%)	FMF patients (*n* = 300)				
	ISSF (*n*%)			Compliance (*n*%)	
	Mild (*n* = 38)	Moderate (*n* = 257)	Severe (*n* = 5)	Compliant (*n* = 244)	Not (*n* = 56)
Headache	19 (50)	112 (43.6)	5 (100)	94 (38.5)	42 (75)
	p < 0.0001			***p < 0.0001***	
Paresthesia	12 (31.6)	60 (23.3)	4 (80)	50 (20.5)	26 (46.4)
	p = 0.01			***p < 0.0001***	
Convulsions					
Febrile	3 (7.9)	13 (5)	1 (20)	16 (6.6)	1 *(1.8)*
Epilepsy	*0 (0)*	*6 (2.3)*	*1 (20)*	*6 (2.4)*	1 (1.8)
	p = 0.07			*p = 0.39*	
Tremors	3 (78.1)	20 (7.7)	4 (80)	20 (8.2)	7 (12.5)
	p < 0.0001			*p = 0.31*	
Breath holding	4 (10.5)	26 (10.1)	1 (20)	32 (13.1)	2 (3.5)
	p = 0.001			*p = 0.06*	
Syncope	1 (2.6)	12 (4.7)	2 (40)	14 (5.7)	1 (1.8)
	p = 0.017			*p = 0.32*	

FMF familial Mediterranean fever, *ISSF* international severity scoring system for FMF. Spearman coefficient, bold values are significant at $p \leq 0.05$

11.5% of children with FMF [23]. In contrast, headache was detected in 3.4% of patients in an Egyptian study that included pediatric and adult FMF patients [28]. Headache is a common symptom in children with rheumatic diseases and may be related to chronic inflammation. Headache frequency was higher among FMF patients with compound heterozygous gene mutation (65.2%), followed by patients with negative FMF mutations (62.5%). In the present cases, there was a relation between headache and disease severity, as headache affected all FMF patients with severe ISSF scores. Headache was the most frequently reported symptom among the colchicine non-compliant patients.

In this study, 25.3% had paresthesias, which was higher than the results obtained by Kalyoncu et al. in 11.1% of cases [8]. The frequency was comparable to that from an Iranian FMF cohort reporting paresthesia in 22% [29]. Parathesis was more common among FMF patients with compound heterozygous MEFV gene mutation and affected 80% of patients with severe ISSF scores and 46% of colchicine non-compliant patients.

Epilepsy was diagnosed in 2.3% of patients during illness, and this is in accordance with Salehzadeh et al. [29] and Bektas et al. [23]. The inflammatory dysregulation may lead to abnormal neural connectivity and hyperexcitability in the neuronal network that mediates

the onset of epilepsy [30]. In contrast, epilepsy was detected in 0.5% of Armenian FMF children [31].

Febrile convulsions and FMF share common molecular pathways such as increased production of IL-1B [32]; in this study, febrile convulsions were detected in 5.7% of patients; this is lower than febrile convulsions reported in general children in an Egyptian study, which was estimated to be 8.8% [33]. On the contrary, febrile seizure in Turkish children with FMF was found to be higher than in the general population [9]. Differences may be related to different genetic backgrounds between diverse populations and sample sizes.

The frequency of breath-holding attacks in healthy children ranges between 0.1 and 4.6% [34], while among FMF patients included in this work was 11.3%. Salehzadeh et al. found that breath-holding attacks were higher in FMF patients than in the normal population [29]. Breath-holding attacks affected 25% of FMF patients with negative FMF gene mutation. It is considered an autonomic dysfunction detected in many rheumatic diseases.

The most prevalent mutation among our patients was heterozygous mutation, which is consistent with the findings of Farag et al. [35]. Abdominal pain was the most frequent manifestation among our patients in 96.3%; this is consistent with Farag et al., in which abdominal pain was the most prevalent symptom [36]. Another Turkish study showed that fever was the commonest symptom among FMF patients [37]; these differences may be related to different ethnicities and genetic mutations.

Serum amyloid A was elevated in 33.7% of the present cases; this is less than the results obtained by Lotfy et al. among Egyptian FMF patients who reported elevated levels in 78.9% due to poor compliance of their patients to colchicine [38]. Such a decrease in the frequency of FMF patients with elevated serum amyloid A may be due to increased awareness about FMF in Egypt, increased availability of colchicine, and successful trials to improve colchicine tolerance and compliance among Egyptian children with FMF. CRP was positive in 16.3% of cases, possibly due to recruiting FMF patients in an attack or an attack-free period.

Neurological outcomes and morbidities in children with FMF have not been systematically investigated. Early detection of neurological affection in FMF children offers a unique opportunity for proper treatment to contribute significantly to the patient's quality of life and to improve the neurodevelopment of FMF children.

The limitation of this study was the relatively small sample size. A large-scale longitudinal study design including different ethnic groups is required to detect the frequency of neurological affection in FMF children precisely and to confirm any relation to other disease parameters. Moreover, a multidisciplinary approach is necessary for better outcomes for FMF patients.

In conclusion, headache and paresthesia were the most common neurological manifestations detected in Egyptian children with FMF. Neurological manifestations among FMF patients are common in patients with severe FMF, compound heterozygous mutations, and patients who were not compliant with colchicine. During routine follow-up visits, clinicians must be suspicious of any neurologic symptoms. Genetic testing should be requested in children with persistent unexplained neurological manifestations, accompanied by symptoms of polyserositis or elevated inflammatory markers and serum amyloid A. Prospective case–control studies may aid in elucidating the pathophysiology underlying FMF's neurologic signs and symptoms.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
CNS	Central nervous system
CRP	C-reactive protein
FMF	Familial Mediterranean fever
MEFV	Mediterranean fever
PRES	Posterior reversible leukoencephalopathy
NLRP3	NLR family pyrin domain containing 3
TNFRSF1A	Tumor necrosis factor receptor superfamily of proteins 1A

Acknowledgements

We thank all the patients included in this study.

Authors' contribution

We the undersigned declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

Funding

The authors received no specific funding for this work.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Pediatric Department Committee for Post-Graduate Studies and Research, Faculty of Medicine, Cairo University, Egypt, approved the study (MS 223–2021). Informed consents were obtained from the participants' legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 28 March 2024 Accepted: 1 June 2024
Published online: 17 June 2024

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