

REVIEW

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Neurological involvement in children with familial Mediterranean fever: a systematic review

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Abstract

Background Although typical findings of familial Mediterranean fever (FMF), such as brief fever episodes and abdominal or chest pain, have been largely described, little is known about the neurological manifestations of the disease in childhood.

Methods A systematic search of the literature was conducted in PubMed/Medline, Cochrane, and Web of Science databases in accordance with the PRISMA guidelines, using MeSH terms related to FMF and neurological manifestations. Studies involving patients under 18 years of age diagnosed with FMF with neurological manifestations were included.

Results Sixty-four studies, comprising 4753 children with FMF, were included. Approximately 33.9% of them had some degree of neurological involvement. Headache was the most common neurological symptom and was often associated with FMF flares, with frequencies ranging from 4.8 to 58.8%. Febrile seizures were also relevant manifestations, as expected in children with FMF since they have more and more high fever during childhood, with frequencies ranging from 1 to 15.2%. Demyelinating disorders, such as multiple sclerosis, were rarely reported, mostly in female adolescents with the homozygous M694V *MEFV* genotype. A few studies have shown that cochlear and retinal involvement due to chronic and recurrent inflammation may contribute to sensorineural hearing loss and retinal abnormalities.

Conclusion Although causality has not been shown and reporting bias cannot be excluded, neurological involvement appears relatively common in children with FMF and may lead to long-term disability and reduced quality of life. These findings support the need for a comprehensive neurological assessment to enable early detection, appropriate management, and better long-term outcomes.

Keywords Familial Mediterranean fever, Neurological involvement, Headache, Seizures, Epilepsy

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Introduction

Familial Mediterranean fever (FMF) often presents in childhood, with high-grade fever lasting 1–3 days, abdominal pain, chest pain, and arthritis due to periodic autoinflammatory attacks and/or recurrent sterile serositis [1–4]. Abdominal pain, thoracic pain, arthritis, and the fever episodes were incorporated into the current EuroFever/PRINTO classification criteria, which is the first set considering the *MEFV* genotype for the diagnosis [2]. Although headaches and other neurological symptoms are often reported by patients during clinical practice and in several reports, little is known about their frequency, characteristics, and management [5–11]. Furthermore, potential impact of the chronic inflammation on the nervous system remains unclear. There are also some reports suggesting the association between FMF and demyelinating disorders such as multiple sclerosis, but their frequency is unknown [12–14]. Therefore, despite the clinical recognition and description of neurological symptoms in FMF, there is a lack of systematic data on their prevalence and nature in the pediatric population, and no comprehensive review has yet addressed this gap. The aim of this systematic review was to evaluate the neurological involvement in children with FMF.

Methods

We conducted a systematic review of the literature according to the PRISMA guideline (Fig. 1). Prior to the beginning, the study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration n. CRD42024512281). To retrieve all relevant articles, a search was performed in PubMed/Medline, Web of Science, and Cochrane databases. The search was structured into two concept blocks:

- FMF-related terms, including historical and alternative nomenclatures.
- Neurological terms, encompassing both general and specific neurological conditions, including those related to headache, seizures, demyelinating disorders, sensory system, and others.

The full search strings for PubMed/Medline-Web of Science, and Cochrane databases are available as *supplementary material S1*. The search involved the articles published in English up to March 1st, 2025, with no filter set for publication date. After manually removing duplicates through an online platform (<https://www.rayyan.ai>), three independent investigators (ADL, GS, and SLB) screened titles and abstracts for eligibility to exclude those irrelevant to the topic. Then, three

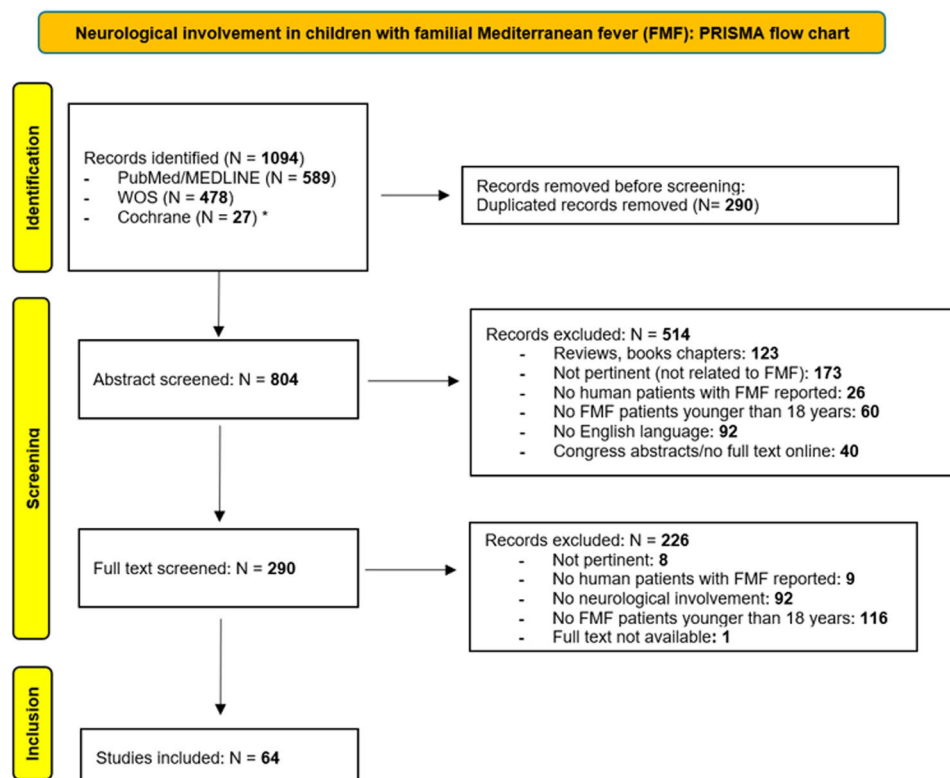


Fig. 1 Flow-chart diagram detailing the selection process according to PRISMA guidelines. The *full search string is available as supplementary material

independent investigators (SLB, MR and YB) assessed the full-text articles. Controversies were resolved by a fourth author (DB). The reference list of each article was also screened for relevant titles. We selected papers detailing FMF patients with less than 18 years of age with clinical neurological involvement or assessing neurological outcomes. All study designs were considered, including case series and case reports. When there was a clear distinction between patients aged less than 18 years and adults, only pediatric patients were included in the dataset. Given the multiple classification criteria available for FMF, all patients diagnosed based on the authors' decision were included. Non-peer reviewed content such as congress abstracts, papers published in languages different than English, and papers not distinguishing between pediatric and adult patients were excluded. The following data were extracted from the articles: first author name, demographic data, study design, FMF classification criteria, characteristics of neurological involvement, *MEFV* genotype, diagnostic work-up, treatment, and outcome. The included studies were analyzed by using Joanna Briggs Institute (JBI) critical appraisal tools (available at: <https://synthesismanual.jbi.global/>). The JBI tools include 8–10 items according to study type (cohort and cross-sectional studies were assessed as observational studies). Scores were: “yes” (meets the qualification), “no” (do not meet the qualification), “unclear/partial” (some information, but not enough to be considered as a yes), and not applicable (NA). Tables were created for each study type (available as *Supplementary material S2*) and color codes; yes = green, no = red, unclear = yellow were used; NA was used if the item was not applicable. In general, most of the included studies had moderate-high quality.

The primary study endpoint was to detail the frequency and characteristics of neurological diseases and manifestations among children with FMF, including those pertaining to peripheral and cranial nerves, such as sensorineural hearing loss, optic nerve disorders, and retinal abnormalities. Articles were classified into six categories: headache, seizures, demyelinating disorders, optic/retinal abnormalities, cochlear/vestibular abnormalities, and other manifestations [13, 15–22].

Results

Patients and studies

After the screening process, we included 64 studies reporting neurological involvement and encompassing 4753 children with FMF. The studies varied in design, ranging from case reports and case series (14/64 and 24/64, respectively) to case-control studies (9/64), and observational studies (17/64). Sample sizes ranged from individual cases to large studies exceeding 600 patients, with children age ranging from infancy to adolescence. Among these children, approximately 1610 (33.9%) had

some degree of neurological involvement. A formal meta-analysis was not conducted due to substantial heterogeneity among the included studies in terms of design, sample size, outcomes assessed, and the criteria used for diagnosing FMF and defining neurological involvement. While some studies focused exclusively on specific symptoms, others detailed a broader spectrum of neurological conditions. In addition, patient populations differed in age, genetic background, and geographic location. These variations may influence the reported prevalence and nature of neurological manifestations and should be considered when interpreting the findings.

Headache

Headache emerged as the most common neurological symptom in children with FMF, affecting 765 (female to male ratio: 1.28) out of 3142 children (24.3%) from 25 studies (Table 1). Not considering case reports and case series, the frequency ranged from 4.8 to 58.8% across the largest studies [6, 8, 15, 16, 18, 23–33]. Reports describe various headache phenotypes, ranging from primary headaches, including migraine with and without aura (107 children diagnosed with migraine and 73 with probable migraine) and tension-type headaches (TTH), to secondary headache syndromes such as pseudotumor cerebri and cerebral vasculitis. In some studies, headache occurred exclusively during FMF attacks [24, 29, 34]. However, none of the reports had a disease control group with a recurrent fever or inflammatory syndrome. In the aforementioned reports, some patients experience a reduction in headache frequency with colchicine and anti-IL-1 drugs, based on observational data [8, 32, 34, 35]. In the study by Güzin et al., headache localization differed by age, being more frequently frontal in patients aged less than 12 years and temporal in older children ($p=0.011$). Moreover, according to the authors, the prevalence of migraine across children with FMF was higher than that in the general Turkish population [15]. In a large study, Abu Shady et al. reported that headache was a common symptom, affecting 45.3% of patients, and that it was associated with FMF disease severity [25]. According to Uluduz et al., the mean duration of headache attacks was longer in children with migraine and probable migraine compared to children with TTH (24 [1Q–3Q: 9.75–36] months vs. 12 [1Q–3Q: 6–24] months, $p=0.029$), with no differences in terms of the frequency of the episodes [16]. Moreover, the highest localization of headache for both FMF patients with migraine and TTH patients occurred in the forehead and occipital regions [16]. Some authors reported that the prevalence of migraine/probable migraine in this population was significantly higher than the prevalence of TTH ($p<0.001$) [5]. Again, these studies failed to provide control groups or follow-up assessments. Biro et al. reported a greater

Table 1 Headache in children with familial Mediterranean fever (FMF), intravenous Immunoglobulins (IVIg), magnetic resonance imaging (MRI), not specified (NS), tension-type headache (TTH)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Underlying cause	Headache type	MEFV genotype	Associated features	Treatment and outcome
Güzin et al., 2025	Yalcinkaya-Ozen	Observational study	148 (83 F, 65 M)	Overall: 78 Migraine: 19 (11 F, 8 M) Other types: 59 (NS)	NS	NS	36 non-specific, 23 TTH, 19 migraine (12 with aura, 7 without aura)	Migraine (n = 19): M694V/M694V (n = 3), E148Q/- (n = 4), E148Q/E148Q (n = 1), M694V/- (n = 2), M694V/M680I (n = 1), M694/R202Q (n = 1), V726A/- (n = 1), M680I/- (n = 1), R202Q/- (n = 1), others (n = 2), no mutation (n = 2)	NS	Headaches were more frequently frontal in patients under 12 years of age and temporal in those aged ≥ 12 years (p = 0.011). 19 patients (12.8%) had definite migraine, and 8 patients (5.4%) had probable migraine, and the prevalence of definite migraine was higher than the population data.
La Bella et al., 2024	Eurofever/PRINTO	Observational study	48 (28 F, 20 M)	22 (NS)	NS	No	NS	NS	NS	7 patients had headache during flares at onset (14.6%) and 22 overall (45.8%). Mild disease severity and good control with colchicine and anti-IL1 were observed
Abu Shady et al., 2024	Yalcinkaya-Ozen	Observational study	300 (158 F, 142 M)	136 (NS)	NS	No	NS	NS	NS	Headache was the most common symptom in 136 (45.3%) patients. There was a relation between headache and disease severity, as headache affected all FMF patients with severe ISSF scores
Ariga et al., 2024	Tel-Hashomer	Case report	1 (M)	1 (M)	15 years	No	NS	P369S/R408Q	Pseudopolyposis/like mucosal changes in the ileum	Improvement was observed after administration of colchicine
Biro et al., 2022	Tel Hashomer	Case-control	111 (47 F, 64 M) Compared with 94 healthy siblings	44 (NS)	NS	No	NS	NS	NS	Authors found a higher prevalence than in healthy siblings: 44 (39.6%) vs. 13 (13.8%), p < 0.001

Table 1 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Underlying cause	Headache type	MEFV genotype	Associated features	Treatment and outcome
Bektas et al., 2022	Yalcinkaya-Ozen	Observational study	625 (320 F, 305 M)	72 (NS)	NS	Yes, in 10 patients (one with idiopathic intracranial hypertension, nine with cause not specified)	Migraine in 27 children, chronic daily headaches in 18 children	NS	NS	NS
Piskin et al., 2022	Yalcinkaya-Ozen and Tel-Hashomer	Observational study	239 (133 F, 106 M)	126 (NS)	NS	No	NS	NS	NS	Headache was documented in 52.7% of the cases
Kurt et al., 2020	Yalcinkaya-Ozen	Case series	25 (14 F, 11 M)	2 (NS)	NS	Anakinra use	NS	NS	NS	Termination of anakinra treatment and switch to canakinumab resulted in absence of further episodes
Demir et al., 2020	Yalcinkaya-Ozen	Observational study	634 (336 F, 298 M)	59 (NS)	NS	No	NS	NS	NS	Headache was documented in 9.3% of the cases
Salehzadeh et al., 2020	Tel-Hashomer	Case series	35 (17 F, 18 M)	3 (2 F, 1 M)	NS	NS	Migraine	E148Q/- (n = 2), A744S/- (n = 1)	NS	A dedicated paper detailed neurological manifestations, but it was excluded because children are not distinguished by adults.
Zerkaoui et al., 2018	Tel-Hashomer	Case report	1 (F)	1 (F)	NS (10 years at occurrence of the acute episode)	Cerebral venous thrombosis of the junction and the sigmoid sinus	NS	M693K	Papillary edema, Behcet disease	The child also had Behcet disease and a history of headaches. Pulse and oral prednisone, enoxaparin sodium, and oral acenocoumarol resulted in good improvement
Eidlitz-Markus et al., 2017	Tel-Hashomer and ICDIII beta version	Observational study	7 (NS)	7 (NS)	NS	NS	Migraine (N = 6) TTH (N = 1)	NS	NS	Authors examined the presence of FMF in pediatric patients diagnosed with headache in a headache clinic. FMF was found six times more often in the migraine group than the tension-headache group (6/200 for migraine and 1/201 for tension headache). However, the between-group difference was not significant.

Table 1 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Underlying cause	Headache type	MEFV genotype	Associated features	Treatment and outcome
Canpolat et al., 2017	Tel-Hashomer	Case series	104 (47 F, 57 M)	16 (9 F, 7 M)	Mean age at diagnosis of FMF was 7.2 ± 3.4 years. Mean interval between the diagnosis of FMF and headache was 3.0 ± 1.5 years	Pseudo-tumour cerebri ($n=2$), epilepsy ($n=1$), multiple sclerosis ($n=1$)	Acute recurrent headache ($n=11$), chronic daily headache ($n=1$), associated to neurologic conditions ($n=4$)	Details for 3 patients (E148Q/- in 2 children, M694V/- in one child)	Dizziness, diplopia, papilloedema and vomiting in the two patients with pseudotumor cerebri	Headache occurred only during attacks in 11 patients and did not accompany every attack. A significant reduction in the frequency of headache attacks was observed during the follow-up period
Çomak et al., 2015	Tel-Hashomer	Observational study	97 (43 F, 54 M)	5 (NS)	NS	No	NS	NS	Febrile seizures in 3 patients	The frequency of headache was higher in febrile seizure positive patients ($p < 0.014$) than those negative, but the small number of patients was not sufficient to make a causal relationship
Jarjour et al., 2015	Tel-Hashomer	Observational study	103 (52 F, 51 M)	5 (NS)	NS	No	NS	M694V/M694V ($n=1$), M694V/other ($n=1$), unknown ($n=3$)	NS	Headache was reported in 4.8% of the sample
Ululuz et al., 2014	NS	Observational study	378 (196 F, 182 M)	173 (96 F, 77 M) classified as follows: 51 (29.5%): migraine; 65 (37.6%): probable migraine; 57 (32.9%): TTH	Migraine: 11.06 ± 2.64 years TTH: 10.73 ± 2.91 years	No	Migraine and TTH	NS	NS	The mean duration of headache attacks was significantly longer in children with migraine and probable migraine than children with TTH (24 [IQ-3Q: 9.75-36] vs. 12 [IQ-3Q: 6-24] months, $p = 0.029$). The frequency of headache was similar in children with TTH and migraine ($p = 0.55$). For FMF patients the localization of the headache was predominantly in the forehead and occipital region in both migraine and TTH patients. <i>Eidiliz-Markus et al</i> calculated that the prevalence of migraine/probable migraine in this population was significantly higher than the prevalence of tension headache ($p < 0.001$)
Per et al., 2013	Dandy (for pseudotumor cerebri)	Case series	2 (1 F, 1 M)	2 (1 F, 1 M)	Patient n.1 (F): 10 years Patient n.2 (M): 12 years	Pseudo-tumour cerebri	Acute recurrent headache	NS	NS	The girl was treated with topiramate for 8 months, and the boy with topiramate and acetazolamide for 24 months, with no recurrence

Table 1 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Underlying cause	Headache type	MEFV genotype	Associated features	Treatment and outcome
Koybasi et al., 2012	Tel-Hashomer	Case-control	34 (17 F, 17 M) compared for cochlear involvement with 27 age matched children	20 (NS)	NS	NS	NS	NS	NS	Headache was reported in 58.8% of the sample
Alenazi et al., 2012	NS	Case series	17 (5 F, 12 M)	3 (NS)	NS	NS	NS	NS	NS	Headache was reported in 17.6% of the sample
Cantarini et al., 2010	NS	Case series	1 (1 M)	1 (1 M)	10 years	NS	NS	R202Q/R202Q	NS	At the age of 15 the patient developed a vacuolar myopathy with intense myalgia and muscle weakness, which recovered after discontinuation of colchicine
Inal et al., 2009	Tel-Hashomer	Observational study	124 (58 F, 66 M)	10 (NS)	NS	NS	NS	NS	NS	In this study, headache was a common (8.1%) finding in children with FMF. Authors suggest that FMF patients should be interrogated about associated symptoms such as headache.
Calligaris et al., 2008	NS	Case report	1 (F)	1 (F)	NS	NS	NS	NS	NS	Headache occurred during attacks under colchicine. Good control with anakinra.
Yucesan et al., 2004	NS	Case report	1 (F)	1 (F)	14 years	NS	Migraine with aura	NS	NS	The patient developed multiple sclerosis at the age of 32 years. The MRI showed multiple periventricular and juxtacortical hyperintense lesions. Good improvement was observed with pulse steroid regimen.
Gedalia et al., 1993	Tel-Hashomer	Case series	101 (55 F, 46 M)	10 (NS)	NS	NS	NS	NS	NS	Headache occurred during attacks. Prevalence was 9.9%
Elakim et al., 1961	NS	Case series	5 (3 F, 2 M)	2 (1 F, 1 M)	NS	NS	NS	NS	NS	The female patient had some abnormalities at the EEG in the interval between attacks

Table 2 Epilepsy and febrile seizures in children with familial Mediterranean fever. Abbreviations: Antiseizure medications (ASMs), familial Mediterranean fever (FMF), electroencephalography (EEG), febrile seizures (FS), magnetic resonance imaging (MRI), not specified (NS)

Reference	FMF Classification criteria	Study design	Overall pediatric cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Seizure type	MEFV genotype	EEG	Outcome and comments
Shukla et al., 2024	Tel-Hashomer	Case report	1 (F)	1 (F)	11 years	Epilepsy	A744S/-	Sharp waves and focal slowing over the temporal regions (not specified whether during or between flares)	MRI was unremarkable. The patients developed recurrent headache (probably migraine), alternating weakness involving both sides of her body, seizures during sleep, focal seizures, tonic-clonic seizures. Not completely controlled by colchicine.
Abu Shady et al., 2024	Yalcinkaya-Ozen	Observational study	300 (158 F, 142 M)	Epilepsy: 7 (NS) Febrile seizures: 17 (NS)	NS	Epilepsy and febrile seizures	NS	NS	Epilepsy was diagnosed in 2.3% of patients during illness, and this is in accordance with other reports (Salehzadeh et al. and Bektas et al.)
Biro et al., 2022	Tel Hashomer	Case-control	111 (47 F, 64 M) Compared to 94 healthy siblings	10 (NS)	NS	Febrile seizures	NS	NS	In 8 out of 10, seizures occurred during an FMF attack. Authors found a higher prevalence than healthy siblings (10 (9%) vs. 1 (1%), $p = 0.041$) and general pediatric population (2–5%)
Kılıç et al., 2022	Yalcinkaya-Ozen	Observational study	417 (208 F, 209 M)	35 (NS)	Mean 2 years (range 0.5–5.5)	Febrile seizures	NS	Normal (performed in 15 patients, not specified whether during or between flares)	The frequency of FS in FMF patients was higher than the general Turkish population (8.4% vs. 4.4%) [$p < 0.0001$, OR: 1.99 (CI: 1.4–2.8)]. 8/35 patients received ASMs, 5/35 had a febrile seizure longer than 15 min.
Bektas et al., 2022	Yalcinkaya-Ozen	Observational study	625 (320 F, 305 M)	Epilepsy: 16 (NS) Febrile seizures: 6 (NS)	NS	Epilepsy and febrile seizures	NS	NS	Epilepsy was the most frequent neurologic disease. Except for 4 children, epileptic seizures were idiopathic in 10 patients. The seizures were focal in symptomatic epilepsies
Salehzadeh et al., 2020	Tel-Hashomer	Case series	35 (17 F, 18 M)	3 (1 F, 2 M)	NS	Seizures	M694V/- (n = 1), R761H/M694I (n = 1), M694V/726A (n = 1)	NS	A dedicated paper was delivered for neurological manifestations, but it was excluded because children are not distinguished by adults.
Haytuglu et al., 2019	Tel-Hashomer and EuroFever/PRINTO	Observational study	46 (16 F, 30 M)	7 (2 F, 5 M)	Mean 1.7 ± 0.7 years	Febrile seizures	M694V/- (n = 1), M694V/R202Q (n = 1), R202Q/E148Q (n = 1), M680I/R202Q (n = 1), E148Q (n = 1), E148Q/V726A (n = 2)	NS	The frequency and recurrence rate of FS was 15.2% (7/46) and 57.1% (4/7) in FMF. MEFV exon 2 and exon 10 allele frequencies were not different in patients with and without FS.

Table 2 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Seizure type	MEFV genotype	EEG	Outcome and comments
Canpolat et al., 2017	Tel-Hashomer	Case series	104 (47 F, 57 M)	6 (2 F, 4 M)	7.8 ± 3.2	Epilepsy	E148Q/- (n = 2), M694V/- (n = 1), M694V/M694V (n = 2), M680I/- (n = 1), M680I/M680I (n = 1)	All had an epileptiform activity with a poorly organized background. Some with also a temporal-parieto-occipital (n = 3)/temporal-occipital (n = 1) slowing. Interictal discharges arisen from parietal (n = 1)/parieto-occipital (n = 2)/left (n = 3)/unspecified (n = 1) regions (not specified whether during or between flares).	5/6 patients had a normal brain MRI, one developed posterior reversible encephalopathy syndrome along with an arachnoid cyst (a male with a homozygous M694V variant). Seizures were controlled with ASMs, and all had a good outcome (absence of a relapse during the follow-up period of 6.5 ± 3.1 years)
Çomak et al., 2015	Tel-Hashomer	Observational study	97 (43 F, 54 M)	13 (7 F, 6 M)	Median 23 (range 7–48) months	Febrile seizures	M694V/- (n = 1), E148Q/- (n = 1), P283R/- (n = 1), R202Q/- (n = 2), M694V/M680I (n = 1), R202Q/- (n = 1), R202Q (n = 2), M694V/E148Q (n = 2), M694V/- (n = 2), R202Q (n = 2), M694V/M694V-R202Q-R202Q (n = 1)	EEG was not performed.	The frequency of febrile seizure in FMF patients was 13.4%. Although there was no difference in the overall allele frequency of MEFV variants between febrile seizure positive and negative patients, a higher frequency of exon 2 and a lower frequency of exon 10 were observed in patients with FS. The prevalence of febrile seizures was higher than the general population (13.4 vs. 5%) [<i>p</i> = 0.04, OR: 2.9 (CI: 1.0-8.5)].
Parvez et al., 2015	NS	Case report	1 (F)	1 (F)	Less than 5 years	Febrile seizures	Mutations in exon 3	Interictal bilateral spikes arising from the temporal regions (not specified whether during or between flares).	Two episodes of generalized tonic-clonic seizures associated with high-grade fever, and additional brief similar episodes that got aborted spontaneously. Normal brain MRI. No more episodes after colchicine initiation
Ertekin et al., 2005	Tel-Hashomer	Observational study	52 (30 F, 22 M)	Febrile seizures: 1 (NS), epilepsy: 1 (NS)	NS	Epilepsy and febrile seizures	NS	One patient had simple FS, the other had epilepsy with EEG abnormality (not specified whether during or between flares).	Prevalence of seizures was documented at 3.8% of the sample. There were no differences between M694V heterozygous and homozygous genotypes. Some patients were enrolled prospectively.

Table 2 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Seizure type	MEFV genotype	EEG	Outcome and comments
Gedalia et al., 1993	Tel-Hashomer	Case series	101 (55 F, 46 M)	3 (1 M, 2 F) (NS)	2 less than 5 years, one at 8 months	Febrile seizures	NS	Normal (not specified whether during or between flares).	For the only patient with details, colchicine and ASMs resulted in good control

frequency of headache among patients with FMF than among healthy siblings (39.6% vs. 13.8%, $p < 0.001$) [26].

Although there was no suggestion for causality, there have been case reports for secondary headaches, including idiopathic intracranial hypertension, cerebral venous thrombosis, pseudotumor cerebri, and cerebral vasculitis in FMF [6, 29, 36–38].

Seizures

Epilepsy and febrile seizures were reported in 127 (female to male ratio: 0.78) out of 1890 patients from 12 studies (Table 2). Reports describe a spectrum of seizure types that mostly occur during FMF flares and are rarely accompanied by electroencephalographic (EEG) abnormalities [39]. Depending on the study, febrile seizure rates ranging from approximately 1–15.2%, with some patients experiencing recurrent seizures during FMF attacks [6, 17, 18, 24–26, 40, 41]. In three studies, the prevalence of febrile seizures in children with FMF was compared to that in healthy individuals [18, 26, 41]. Kılıç et al. reported that the frequency of febrile seizures in FMF children was greater than that in the general Turkish population (8.4% vs. 4.4%; OR: 1.99, 95% CI: 1.4–2.8, $p < 0.0001$), as well as and Çomak et al. (13.4% vs. 5% OR: 2.9; 95% CI: 1–8.5, $p = 0.04$) [18, 41]. Biro et al. reported a greater prevalence of febrile seizures in FMF patients than in both healthy siblings (9% vs. 1%, $p = 0.041$) and the general pediatric population (2–5%) [26]. A few studies investigated the impact of the *MEFV* genotype on seizures [17, 18, 40]. Ertekin et al. reported no differences in seizure occurrence between patients carrying heterozygous and homozygous M694V variants, whereas Çomak et al. reported that, although there was no difference in the overall allele frequency of *MEFV* variants between febrile seizure positive and negative patients, those with febrile seizures had a higher frequency of exon 2 variants and a lower frequency of exon 10 variants compared to patients without febrile seizures [18, 40]. Nevertheless, Haytoglu et al. found no differences between *MEFV* exon 2 and exon 10 variant frequencies in FMF children with and without febrile seizures [17]. There is a limited number of reports on pediatric FMF patients with epilepsy and EEG abnormalities, usually including interictal discharges, a poorly organized background activity, and focal slowing over diverse regions; however, the timing of the EEG, whether performed during or between flares, was generally not specified [29, 39, 42]. When performed, brain magnetic resonance imaging (MRI) was unremarkable except for a patient that developed posterior reversible encephalopathy syndrome [29].

Demyelinating disorders

Demyelinating disorders were reported in eight children with FMF (female to male ratio: 6) across seven studies,

with a prevalence in large studies ranging from 0.16 to 0.96% (Table 3) [6, 12–14, 29, 43, 44]. Five children were diagnosed with multiple sclerosis (two children with a relapsing-remitting course, one child with a secondary progressive course and two patients with a not specified course), with a disease onset ranging from 12 to 17 years; notably, four of them (80%) carried the homozygous M694V variant [13, 14, 29, 43]. A female adolescent who presented with acute quadriplegia and pseudobulbar paresis was diagnosed with an unclassifiable demyelinating disorder and was treated with high-dose oral steroids with poor outcomes [12]. A child was diagnosed with transverse myelitis, and a 13-year-old female presenting with blurred vision and dizziness was classified as having a clinically isolated syndrome [6, 13]. Treatment approaches generally consist of high-dose corticosteroids and disease-modifying therapies such as glatiramer acetate.

Retinal and optic nerve involvement

Retinal and/or optic nerve involvement was reported in six studies (Table 4) [19, 20, 45–48]. Among these, some reports were on retinal inflammation, and others have investigated abnormalities in ocular blood flow and retinal or optic nerve structure. Two studies reported bilateral recurrent optic neuritis, both in male toddlers with the homozygous M694V *MEFV* genotype [45, 48]. Both patients presented with a sudden loss of vision and typical findings on orbital MRI, increased bilateral thickness of the optic nerves, and a prolonged latency at the visual evoked potential. Good control was obtained with colchicine, IL-1 inhibitors, and systemic steroids [45, 48]. Mansour et al. described three cases of bilateral retinal vasculitis, with underlying disc edema, retinal hemorrhages, and frosted branch angiitis. Two patients achieved full visual recovery under immunosuppressive agents, while the third patient did not recover vision due to no treatment [46]. Eski et al. reported that, FMF patients had reduced ocular blood flow and choroidal thinning compared to healthy controls [20]. These alterations were identified via optical coherence tomography and color Doppler ultrasonography, with decreased peak systolic and end-diastolic velocities in the central retinal, ophthalmic, and nasal posterior ciliary arteries, alongside increased resistivity indices, suggesting that chronic inflammation may contribute to these vascular changes [20]. Abnormal foveal vascular structure was reported by Yener et al. indicating that patients with FMF had altered vessel density in different quadrants of the parafoveal region compared to controls [47]. In a retrospective study, Kivrak et al. reported that homozygous M694V FMF patients had a reduced peripapillary retinal nerve fiber layer compared to asymptomatic heterozygous M694V carriers, who were not diagnosed with FMF

[19]. None of these studies have suggested a causal relation and the prevalence among the healthy population was not described in most of them. Furthermore, subsequent studies revealed no differences in retinal thickness between children with FMF and controls [49, 50].

Cochlear and vestibular involvement

Cochlear or vestibular involvement, particularly in the form of hearing loss and cochlear dysfunction, was reported in nine studies (Table 5) [6, 21, 22, 31, 51–55]. Sensorineural hearing loss in children with FMF was documented in many of these reports. Talaat et al. suggested that children with FMF seemed to have an increased risk of hearing impairment but documented no significant correlations between the study demographics, genetics, clinical manifestations, disease severity score, and audiological tests [21]. Salimov et al. reported that hearing thresholds were greater in patients with FMF than in controls at most frequencies [22]. Similar results were obtained in case-control studies [31, 52–54]. Sensorineural hearing loss has also been reported in a few series [51, 53]. Notably, bilateral sensorineural hearing loss was described in two children with FMF carrying a complex *MEFV* genotype (I692del/E148Q/V726A) in addition to two different heterozygous variants in the *NLRP3* gene (one with Q703K, the other V198M), classified as variants of unknown significance according to Infervers (<https://infervers.umai-montpellier.fr/web/search.php?n=4>), making very difficult a clear interpretation of the phenotype [55]. Vertigo and dizziness were retrospectively reported in 38 out of 625 children with FMF from a large study, with an underlying cause found in four of them as stroke and cerebral vasculitis [6].

Other manifestations

In addition to the better-defined categories described above, 249 children were reported to have other neurological symptoms in 21 reports (Table 6). These miscellaneous manifestations included sensory disturbances, movement disorders, and various neuromuscular impairments, emphasizing the heterogeneous nature of neurological involvement in children with FMF. A large study revealed 26 patients with sensorial disorders, 16 with muscle weakness, 7 with movement disorders, 2 with cerebrovascular events, cerebral vasculitis, aseptic/viral meningitis, and one with idiopathic intracranial hypertension [6]. An additional large study reported a significant frequency of paresthesia and tremors (76 and 27 out of 300 patients, respectively), peaking at 80% in patients with severe disease [25]. Cognitive impairments, attention, memory, and executive function fragilities, have been investigated and reported by a few studies, with conflicting results [56–58].

Table 3 Demyelinating disorders in children with familial Mediterranean fever. Abbreviations: familial Mediterranean fever (FMF), intravenous Immunoglobulins (IVIg), magnetic resonance imaging (MRI), not specified (NS)

Reference	Classification Criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Type	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Korkmaz et al., 2022	Tel-Hashomer criteria and McDonald criteria	Case series	2 (2 F)	2 (2 F)	Patient n.1: 15 years Patient n.2: 13 years	Patient n.1: Multiple sclerosis Patient n.2: Clinical isolated syndrome	Patient n.1: M694V/M694V Patient n.2: M694V/R202Q	Patient n.1: MRI detected demyelinating lesions in the right and left cingulate gyrus, and in the spinal cord (thoracic 4–6) Patient n.2: demyelinated lesions adjacent to the periventricular region	Patient n.1 presented with numbness in the right and left half of the body and atypical limb pain and was treated with colchicine, anakinra, glatiramer acetate, and pulse steroids. Patient n.2 presented with blurred vision and dizziness and was not treated.
Bektas et al., 2022	Yalcinkaya-Ozen	Observational study	625 (320 F, 305 M)	1 (NS)	NS	Transverse myelitis	NS	NS	NS
Elhani et al., 2021	Tel-Hashomer	Case series	1 (F)	1 (F)	15 years	Relapsing remitting multiple sclerosis	M694V/M694V	Brain MRI detected white matter lesions, and oligo clonal bands were positive	Glatiramer acetate, dimethyl fumarate and interferon beta
Canpolat et al., 2017	Tel-Hashomer	Case series	104 (47 F, 57 M)	1 (M)	12 years	Relapsing remitting multiple sclerosis, postural hand tremors and headache.	M694V/M694V	Brain MRI detected white matter lesions, and oligo clonal bands were negative	High dose of methylprednisolone was initiated, and brain MRI revealed a decrease in plaque size. However, in the second year of control, several plaques were noted and were treated with high-dose steroids.
Yahalom et al., 2011	Tel-Hashomer criteria and McDonald criteria	Case series	1 (F)	1 (F)	17 years	Secondary progressive multiple sclerosis	M694V/M694V	Brain MRI detected multiple white matter lesions, and oligo clonal bands were positive	The patient presented with right hand numbness and probably weakness and was treated with interferon beta, glatiramer acetate, IVIg, and azathioprine
Blashcek et al., 2010	McDonald criteria	Case report	1 (1 F)	1 (1 F)	14 years	Multiple sclerosis	E230K/-	Brain MRI showed multiple hyperintense lesions involving also the brain stem and the spinal cord, and oligo clonal bands were positive	The patient presented with left-sided paraesthesias and impaired hearing, double vision, nystagmus, and impaired balance. Good control with interferon beta and glatiramer acetate
Akman-Demir et al., 2006	Tel-Hashomer	Case series	1 (1 F)	1 (1 F)	17 years	Unclassifiable demyelinating disorder	NS	Brain MRI showed diffuse white matter hyperintensity	The patient presented with acute quadripareisis and pseudobulbar paresis and improvement with high dose oral steroids but passed away for renal failure.

On the other hand, colchicine intoxication resulted in muscle weakness and atonic falls in an 8-year-old female due to concomitant intake of grapefruit juice, whereas colchicine-induced myo-neuropathy was diagnosed in three patients and improved after colchicine discontinuation [59–61]. There are also rare case reports of children with FMF developing dystonia, acute brachial plexopathy, small-fiber neuropathy, reflex sympathetic dystrophy, posterior reversible encephalopathy syndrome, recurrent aseptic meningitis, postural hand tremor, recurrent peripheral facial palsy, hypertensive encephalopathy, intracranial venous occlusive disease, and cerebrovascular disease [7, 23, 29, 62–71].

Discussion

Headache

According to our findings, headache is the most common neurological symptom in children with FMF, with reports detailing different prevalence rates, peaking in more than half of the patients, and diverse headache types, mostly represented by migraine and TTH. Reports also vary in terms of headache timing, with acute recurrent headache being more common than chronic headache. Moreover, in several reports headache episodes occurred only during FMF flares. Interestingly, in a recent study on 300 children with FMF, headaches were more frequent among patients with compound heterozygous mutation, severe disease activity, and poor compliance with colchicine [25]. Moreover, according to a recent multicentric prospective study including 876 patients with FMF, largely children (80.4%), headache was detected in 109 (12.4%) patients at enrollment and was more prevalent in patients with a clinical diagnosis than in those with a supportive *MEFV* genotype [72]. Higher rates of neurological manifestations were described in a large study of 311 children and adults with FMF, with headaches occurring in 47.3% of them (including migraines in approximately 6.1%) [73]. The authors reported some observational evidence that headache was more common in the *MEFV* negative group [73].

Only one study, by Biro et al., included a disease control group and reported a higher prevalence of recurrent headaches in patients with FMF compared with healthy siblings; however, the small sample size (44/111 patients vs. 13/94 healthy siblings), the observational nature of the study and potential biases limit the strength of this evidence [26]. When comparing the prevalence of headache to that in the general population, Güzin et al. identified a higher rate in children with FMF in their patients (12.8%) than that reported in the general population of children and adolescents, where estimated rates range from 7.7% (95% CI: 7.6–7.8) to 9.1% (95% CI: 7.1–11.1), higher in females, with lower rates in children aged less than 7 years [74–76]. More recent data from a systematic

review and meta-analysis conducted in healthy children aged 8–18 years estimated the rate of migraine in this age group at 11% (95% CI: 9–14%) and the rate of TTH at 17% (95% CI: 12–23%). As expected, the overall primary headache rate was higher, estimated at 62% (95% CI: 53–70%) [77]. In other studies (not considering reports with less than 10 patients), migraine rates range from 8.6% [73] to 10.2% [6], and 13.5% [16]. However, data from the included studies are heterogeneous and insufficient to support evidence-based comparisons between children with FMF and healthy controls. Moreover, in several studies the exact type of headache is not specified and the numbers of patients with either migraine or TTH are largely derived by retrospective and monocentric studies. Furthermore, a causal relation has not been suggested.

Only a minority of patients with headaches had an underlying cause, mostly represented by intracranial hypertension, idiopathic hypertension or headaches caused by pseudotumor cerebri or cerebral venous thrombosis. This is likely due to high-grade fever or various degrees of inflammation. Sterile inflammation occurring during disease flares likely affect the meninges, resulting in recurrent sterile meningitis and subsequent headaches of various degrees. However, this has never been shown. Some authors suggest that FMF patients should be interrogated about the presence of headache, and migraine should be considered as a possible diagnosis in headache episodes reported by FMF patients [15, 16].

Seizures

Interestingly, febrile seizures have been reported in several studies, mostly occurring concomitant to disease flares, probably because of the frequent fever episodes experienced in the early years of life. There is some evidence that headaches and febrile seizures may be more common in FMF patients than in the general population. As detailed before, three studies reported that the prevalence of febrile seizures in children with FMF was greater than that in the general pediatric population. In these studies, prevalence of febrile seizures was estimated at 8.4% [41], 9% [26], and 13.4% [18]. Additional data are available from other studies, with prevalence ranging from 1% (Bektas et al.) to 15.2% (Haytoglu et al.) [6, 17, 24, 25, 40]. Notably, the prevalence of febrile seizures in healthy children is estimated to range from 2 to 5%, with a recurrence rate of approximately 25–40%, and variations observed across different ethnic groups [78–81]. Conversely, only one observational report assessed a greater prevalence of febrile seizures in children with FMF than in a control group of healthy siblings (9% vs. 1%, $p=0.041$) [26]. However, these data may not provide sufficient evidence, mainly due to the observational

Table 4 Retinal and optic nerve involvement in children with familial Mediterranean fever. Abbreviations: familial Mediterranean fever (FMF), magnetic resonance imaging (MRI), not specified (NS), optical coherence tomography (OCT)

Reference	Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Kivrak et al, 2023	Tel-Hashomer	Observational study	30 (19 F, 11 M) Compared with 12 asymptomatic heterozygous MEFV M694V carriers and 41 healthy controls	30 (19 F, 11 M)	-	Reduced peripapillary retinal nerve fiber layer and central macular thickness	M694V/M694V (n = 30)	OCT	FMF patients had thinner peripapillary retinal nerve fiber layer than M694V asymptomatic carriers and healthy controls, especially in the inferior quadrant. Moreover, the central macular thickness in FMF was thinner than in M694V asymptomatic carriers (but not than controls), especially the superior and inferior quadrants of macula. Changes of peripapillary retinal nerve fiber layer thickness and central macular thickness in FMF patients were moderately correlated with the duration of diagnosis
Avar-Aydin et al., 2022	Yalcinkaya-Ozen	Case series	512 (NS)	1 (M)	4 years	Bilateral recurrent optic neuritis	M694V/M694V	Visual evoked potentials (prolonged latency) Orbital and cranial MRI with contrast (bilaterally increased thickness and contrast enhancement of the optic nerve)	Sudden loss of vision in both eyes, absent pupillary reflexes and decreased visual acuity in both eyes. No more episodes with anakinra, systemic steroids and colchicine
Eski et al., 2022	Tel-Hashomer	Case-control	56 (29 F, 27 M) Compared with 56 healthy controls	56 (29 F, 27 M)	-	Reduced ocular blood flow and choroidal thickness	NS	OCT (All measurements were thinner in patients with FMF than in the controls except than the Nasal_1500 point) and Color Doppler ultrasonography (the peak systolic velocity and end systolic velocity values in the central retinal artery, ophthalmic artery, and nasal posterior ciliary artery were lower in FMF patients than controls. The resistivity index values of all arteries were higher than in controls	Authors conclude that chronic inflammation and frequent attacks in FMF may influence decreased ocular blood flow and choroidal thinning

Table 4 (continued)

Reference	Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Mansour et al., 2022	Tel-Hashomer	Case series	3 (1 F, 2 M)	3 (1 F, 2 M)	Patient n.1 (F): 9 years Patient n.2 (M): 13 years Patient n.3 (M): 14 years	Bilateral retinal vasculitis	Patient n.1 and n.2: NS Patient n.3: V726A/-	Retinal haemorrhages: patients n.2 and n.3 Disc edema: patient n.2 Frosted branch angiitis: patient n.3. No patients had a cystoid macular edema or vitreous haemorrhage.	Patient n.1: full visual recovery with methotrexate/adalimumab and cyclosporine; patient n.2: full visual recovery with cyclophosphamide and oral steroids; patient n.3: No visual recovery after 2 months of follow-up (no immunosuppressive therapy)
Yener et al., 2021	NS	Case-control	20 (9 F, 11 M) compared with 20 healthy controls	20 (9 F, 11 M)	-	Abnormal foveal vascular structure	NS	Ophthalmologic examination, slit-lamp, dilated funduscopy, OCT: parafoveal temporal quadrant vessel density of patients was higher, and parafoveal nasal quadrant vessel density was lower than that of controls	Authors conclude that FMF may affect foveal vascular structure in children besides multiple other organ involvement.
Başaran et al., 2016	NS	Case report	1 (M)	1 (M)	5 years	Bilateral recurrent optic neuritis that occurred concurrently with FMF episodes	M694V/M694V	Ophthalmologic examination: haemorrhage and swelling of optic disc, reduced visual acuity; visual evoked potential: bilateral significant prolongation (no impulses and the third episode); orbital MRI: bilateral thickness of optic nerves and optic neuritis	The patient presented with a sudden loss of vision. Good control with pulse steroid regimen, canakinumab and colchicine.

Table 5 Cochlear and vestibular involvement in children with familial Mediterranean fever. Abbreviations: auditory brainstem response (ABR), distortion product otoacoustic emissions (DPOAE), distortion product otoacoustic emission response (DPOAR), familial Mediterranean fever (FMF), not specified (NS), pure tone audiometry (PTA)

Reference	Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Talaat et al., 2023	Tel-Hashomer criteria	Observational study	100 (57 F, 43 M)	86 (49 F, 37 M)	-	Unilateral or bilateral hearing loss	21 homozygous, 44 heterozygous, 21 compound heterozygous	PTA, immittance audiometry (tympanometry and acoustic reflex to exclude middle ear dysfunction) and TEOAE	Authors conclude that children with FMF seem to have an increased risk of hearing impairment due to the affection of cochlear functions. No significant correlations were found between the study demographics, genetics, clinical manifestations, disease severity score and audiological tests
Bektas et al., 2022	Yalcinkaya-Ozen	Observational study	625 (320 F, 305 M)	38 (NS)	NS	Vertigo and dizziness	NS	NS	The origin of vertigo was central for 4 children with stroke and cerebral vasculitis.
Llobet-Agulló et al., 2022	Tel-Hashomer criteria	Case series	7 (3 F, 4 M)	1 (F)	NS	Sensorineural hearing loss	Unspecified MEFV variant in heterozygosis	NS	NS
Salimov et al., 2019	Yalcinkaya-Ozen criteria	Case series	40 (21 F, 19 M)	40 (21 F, 19 M)	-	Cochlear involvement	Various (mostly homozygous or heterozygous for M694V)	PTA, DPOAE, ABR	Hearing thresholds of FMF patients than controls were found to be increased at most frequencies. Lower signal/noise ratios were detected at most frequencies in the DPAOE test. A positive effect of treatment of the disease with long term colchicine in hearing was demonstrated.
Andaloro et al., 2018	Tel-Hashomer criteria	Case-control	50 (26 F, 24 M) Compared with 31 healthy controls	50 (26 F, 24 M)	-	Hearing loss	NS	PTA, ABR, DPOAR	Hearing thresholds of FMF patients, compared to the control group, were found to be increased at all frequencies on the left and at 1000, 4000, and 8000 Hz on the right ($p < 0.05$). This was supported by the DPOAE test, with lower values at all frequencies in FMF children ($p < 0.05$)
Lordoglu et al., 2016	Tel-Hashomer criteria	Case-control	50 (26 F, 24 M) Compared with 39 healthy controls	50 (26 F, 24 M)	-	Impaired cochlear functions particularly at high frequencies	NS	PTA, DPOAE	The pure tone average of FMF patients was higher than that controls at 500, 4000, and 8000 Hz frequencies. The patients' DPOAE signal values at 6 kHz, 8 kHz frequencies and SNR values at 8 kHz were higher than controls. Pure tone average was higher in severe and moderate patient groups than the mild patient group at 2000 Hz frequency. DPOAE signal values showed significant differences between the patient severity scores at 1.4 and 2.8 kHz frequencies. There were significant differences at 250 and 500 Hz frequencies when patients' audiometry results were compared with the treatment (colchicine) periods

Table 5 (continued)

Reference	Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Bucak et al., 2014	Tel-Hashomer criteria	Case-control	49 (NS) Compared with 49 healthy controls	49 (NS)	-	Sensorineural hearing loss	NS	Tympanometry and DPOAE	Hearing thresholds of FMF patients were found to be increased at all frequencies than controls (250 to 16,000 Hz) ($p < 0.001$)
Koybasi et al., 2012	Tel Hashomer	Case-control	34 (17 F, 17 M) compared with 27 healthy controls	34 (17 F, 17 M)	NS	Cochlear function impairment	Various (E148Q/-, E148Q/E148Q, M694V/-, V726A/- and others)	PTA, DPOAE	PTA hearing levels were within normal levels. Hearing thresholds of FMF patients were increased at frequencies 8000, 10,000, 12,500 and 16,000 ($p < 0.05$). In otoacoustic emission evaluation, distortion products and signal noise ratio of FMF children were lower in the tested frequencies, from 1400 Hz to 4000 Hz ($p < 0.05$). Interaction of the disease duration and age of disease onset was found to predict hearing levels, distortion products and signal-noise ratios of children with Familial Mediterranean Fever (F value = 2.034; $p = 0.033$). Both patients had variant in the <i>NLRP3/C1AS1</i> gene (patient n.1: Q703K, patient n.2: V198M)
Singh-Grewal et al., 2007	NS	Case series	2 (1 F, 1 M)	2 (1 F, 1 M)	Patient n.1 (M): 5 years Patient n.2 (F): 6 years	Bilateral sensorineural deafness	V726A/I692del/E148Q (n=2)	Audiometry: Patient n.1: sensorineural deafness of 60 dB bilaterally in the 2000–3000 Hz range. Patient n.2: bilateral sensorineural deafness of 60 dB at frequencies of > 1000 Hz with speech delay at 6 years	

Table 6 Other neurological manifestations in children with familial Mediterranean fever. Abbreviations: cerebrospinal fluid (CSF), electroencephalography (EEG), electromyography (EMG), familial Mediterranean fever (FMF), magnetic resonance imaging (MRI), not specified (NS),

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Neurological involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Abu Shady et al, 2024	Yalcinkaya-Ozen	Observational study	300 (158 F, 142 M)	Paresthesia: 76 (NS) Tremors: 27 (NS)	NS	Paresthesia and tremors	NS	NS	Paresthesia and tremors were present in 80% of patients with severe disease
Inalkac Gemici et al, 2024	Yalcinkaya-Ozen	Case series	2 (1 F, 1 M)	2 (1 F, 1 M)	Patient n.1 (female): 14 years Patient n.2 (male): 10 years	Dystonia	M694V/I591T (n=2)	Brain MRI and EMG; negative	Both patients had diabetes mellitus type 1. The male patient experienced generalized dystonia prominent in the cervical region and was treated with levodopa, trihexyphenidyl, and botulinum toxin injections. The female patient experienced writer's cramp and was treated with botulinum toxin injections. In addition to the MEFV compound heterozygosity, the patients also carried the heterozygous R505* variant (possibly pathogenic) in the <i>VP516</i> gene, which is responsible for a clinical phenotype characterized by dystonia

Table 6 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Neurological involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Bektas et al., 2022	Yalcinkaya-Ozen	Observational study	625 (320 F, 305 M)	Sensation disorders: 26 Muscle weakness: 16 Movement disorders: 7 Cerebrovascular event: 2 Cerebral vasculitis: 2 Aseptic/viral meningitis: 2 Idiopathic intracranial hypertension: 1 (also present in Table 1 as cause of secondary headache)	NS	Various (sensation disorders, muscle weakness, movement disorders, cerebrovascular events, cerebral vasculitis, aseptic/viral meningitis, idiopathic intracranial hypertension)	NS	NS	Overall, 142 (23.5%) of patients experienced neurological symptoms, higher than previous studies.
Kasap-Demir et al., 2022	NS	Case report	1 (M)	1 (M)	14 years	Bilateral acute brachial plexopathy	M694V/M694V	EMG: bilateral acute brachial plexopathy	The patient developed PAN-associated perirenal haematoma
Shinkarevsky Fleitman et al., 2020	Tel-Hashomer	Case series	3 (3 F)	3 (3 F)	Patient n.1 17 years Patient n.2 15 years Patient n.3 9 years	Small-fiber neuropathy (headache, fibromyalgia, learning problems, autonomic dysfunction)	Patient n.1: E148Q/R408Q/A457V/P369S; Patient n.2 M694V/M694V; Patient n.3 E148Q/-	Skin biopsy	Patients were diagnosed with small-fiber neuropathy and erythromelalgia. Improvement was observed with proper treatment.
Demir et al., 2020	Yalcinkaya-Ozen	Observational study	634 (336 F, 298 M)	2 (NS)	NS	Reflex sympathetic dystrophy	NS	NS	Reflex sympathetic dystrophy was found in 0.3% of the sample

Table 6 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric FMF affected (sex)	Onset of neurological manifestations	Neurological involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Keskin-demirci et al., 2018	Tel-Hashomer	Case-control	12 (6 F, 6 M) Compared with 12 healthy controls	12 (6 F, 6 M)	-	Strong allocation of attention and working memory capacity	Al: M694V/ M694V (four patients also had additional variants)	The amplitude of the P300 (the cognitive component of the electrophysiologically event-related potentials or electrophysiologically event-related potentials) of the FMF patients was higher than controls ($13.326 \pm 7.25 \mu V$ vs. $12.15 \pm 5.91 \mu V$, $p = 0.025$)	Cognitive processing reflecting allocation of attention and visual processing speed seem not to be negatively affected in FMF patients.
Özer et al., 2017	Tel-Hashomer	Case-control	52 (24 F, 28 M) Compared with 36 healthy controls	52 (24 F, 28 M)	-	Worse cognitive abilities than controls	NS	Various neurocognitive tests comprised in the "Central Nervous System Vital Signs"	Authors found impaired neurocognitive profiles in the FMF children than controls
Yusef et al., 2017	NS	Case report	1 (M)	1 (M)	13 years	Recurrent aseptic meningitis	E148Q/E148Q	CSF analysis revealed white blood cell count of 45 cells/ μL with 97% lymphocytes; protein, 27 mg/dL; and glucose, 80 mg/dL. The CSF culture was negative. CSF tests for enteroviruses and herpes simplex virus were negative.	Good control with colchicine
Canpolat et al., 2017	Tel-Hashomer	Case series	104 (47 F, 57 M)	2 (2 M)	6 years and 12 years	Postural hand tremor	M694V/M694V ($n = 1$) and R202Q/P369S ($n = 1$)	In the first patient the brain MRI revealed multiple sclerosis; in the second patient brain MRI was negative	The first patient was diagnosed with multiple sclerosis and treated with high-dose steroids. The second patient developed hand tremors after an attack of IgA vasculitis at the age of 6 years
Gülhan et al., 2013	NS	Case series	1 (F)	1 (F)	-	Mild cognitive impairment	E148Q/E148Q	NS	NS
Yılmaz et al., 2013	NS	Case report	1 (F)	1 (F)	14 years	Right recurrent peripheral facial palsy (Bell palsy)	M694V/M694V	Electrophysiologic studies of the facial nerve were not performed because the patient showed rapid recovery from all episodes	Authors concluded that recurrent peripheral facial palsy might be a manifestation of FMF
İşıkay et al., 2013	NS	Observational study	88 (47 F, 41 M)	1 (M)	13 years	Mild carpal tunnel syndrome	NS	Nerve conduction studies: low sensorial nerve conduction rates in the palm/wrist segment of the median nerve in both hands	The study aimed to investigate frequency of neuromyopathy in a cohort of FMF children taking colchicine.

Table 6 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric affected (sex)	Onset of neurological manifestations	Neurological involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Kalyoncu et al., 2010	Tel Hashomer	Case series	2 (1 F, 1 M)	2 (1 F, 1 M)	Patient n.1 (male): 9 years Patient n.2 (female): 16 years	Posterior reversible encephalopathy syndrome	M694V/M694V (n = 2)	Patient n.1: Bilateral cortical edema in posterior hemispheres, anterior watershed areas, and left cerebellum; EEG showed right temporoparieto-occipital background slowing and epileptiform activity. Patient 2: Bilateral occipital, parietal, and posterior frontal cortical edema; EEG showed mild bilateral background slowing	Patient n.1 presented with focal convulsions and was treated with anti-hypertensive and phenytoin. Patient n.2 presented with generalized tonic clonic convulsion and was treated with hypertensive and phenobarbital
Cantarini et al., 2010	NS	Case series	1 (1 M)	2 (1 F, 1 M)	Patient n.1 (female) 3 years Patient n.2 (male) 7 years	Cerebrovascular disease	M694V/M694V (n = 2)	Patient n.1: Brain MRI showed chronic lacunar infarct in right thalamus; EMG documented dystonic discharges on left side. Patient n.2: Brain MRI showed a right middle cerebral artery occlusion, acute ischemic lesion in right basal ganglion and a thin, acute subtentorial subdural hematoma	Patient n.1 presented with incoordination on left side and was not treated. Patient n.2 presented with left-sided paresis and was treated with acetylsalicylic acid
Özkaya et al., 2007	NS	Case series Case report	1 (1 M) 1 (F)	1 (1 M) 1 (F)	15 years 10 years	Colchicine neuromyopathy Cerebral vasculitis in IgA vasculitis	R202Q/R202Q M694V/M694V	Muscle biopsy: vacuolar myopathy Initial brain MRI: areas of increased signal in bilateral frontoparietal and especially parietooccipital regions. EEG: normal.	The patient presented with muscle weakness and recovered after discontinuation of colchicine The patient presented with generalized seizures and was treated with intravenous pulse methylprednisolone followed by oral prednisolone and cyclophosphamide. Complete resolution of the cerebral lesions after 30 days.
Ozyurek et al., 2005	NS	Case series	1 (F)	1 (F)	16 years	Posterior reversible encephalopathy syndrome	Homozygous MEFV mutation	Brain computed tomography scan was normal; the brain MRI showed parieto-occipital cortical and subcortical edematous lesions	The patient developed hypertension, headache and generalized tonic-clonic seizures; the cause was considered to be hypertension

Table 6 (continued)

Reference	FMF Classification criteria	Study design	Overall pediatric FMF cohort (sex)	Pediatric affected (sex)	Onset of neurological manifestations	Neurological involvement	MEFV genotype	Diagnostic exams performed	Treatment and outcome
Goldbart et al., 2000	NS	Case report	1 (F)	1 (F)	8 years	Atonic falls and weakness due to colchicine and grapefruit interaction	NS	EEG: normal	The clinical picture was caused by the interaction between colchicine and grapefruit.
Harel et al., 1998	NS	Case series	2 (1 F, 1 M)	2 (1 F, 1 M)	Patient n.1 (male): 5 years Patient n.2 (female): 16 years	Colchicine-induced myoneuropathy	NS	EMG: Patient n.1: distal sensory latency, increased recruitment pattern, reduced amplitude and short duration motor unit potentials. Patient n.2: reduced motor nerve conduction velocity and increased distal latency.	Improvement after colchicine discontinuation
Najim al-Din et al., 1994	NS	Case series	1 (M)	1 (M)	16 years	Intracranial venous occlusive disease	NS	NS	The patient presented with signs and symptoms of increased intracranial pressure lasting 4 weeks
Ozen et al., 1965	NS	Case report	1 (M)	1 (M)	8 years	Hypertensive encephalopathy	NS	NS	The patient presented with headache, vomiting, convulsions and unconsciousness, and died for hypertensive encephalopathy.

nature of the studies and differences in the prevalence of these manifestations across countries, ethnic groups, and ages [18, 26, 82]. Febrile seizures, however, are expected to be more frequent in children with FMF, since they experience recurrent episodes of high fever during childhood. Furthermore, their fever is often more severe and more resistant to antipyretics.

Epilepsy with EEG abnormalities is rarely reported, often with limited details, and it does not seem to be directly related to FMF in pediatric patients.

Demyelinating disorders

Demyelinating disorders have been rarely reported in children with FMF, mostly occurring in female adolescents with the M694V homozygous *MEFV* genotype. It is possible but still unclear whether a pathogenic genotype and a high severity of recurrent and/or chronic subclinical inflammation may trigger the immune system and demyelinating disease onset. Indeed, some inflammatory diseases such as juvenile idiopathic arthritis, IgA vasculitis, polyarteritis nodosa, and spondyloarthritis, have been associated with FMF [83–85]. However, due to the limited number of pediatric FMF patients with multiple sclerosis, further studies are needed to better clarify this phenomenon. Notably, studies with also adult FMF populations have suggested a possible, though not conclusive, link between innate inflammation in FMF and other inflammatory diseases, including multiple sclerosis. However, this relation appears not to be strictly influenced by the *MEFV* genotype [12, 13, 85].

Retinal/optic nerve and cochlear/vestibular involvement

A few studies investigated cochlear and retinal involvement in affected patients, with some evidence that inflammation may cause abnormalities in retinal structure, ocular blood flow, and sensorineural hearing loss. However, there was no suggestion of a causal relation in these reports. Furthermore, these reports may represent simple reporting bias since these patients have FMF and they may be just coincidental findings. There are also additional studies not confirming such results and finding no differences in hearing thresholds between children with FMF and healthy controls [86–88].

Other manifestations

A number of case reports detailed a wide range of additional neurological manifestations in children with FMF. There is a lack of data supporting cognitive involvement in affected patients, with studies reporting conflicting results in differences among cognitive abilities compared with healthy controls [26, 56, 57].

Potential role of IL-1 β in neuroinflammation of FMF

One of the key mechanisms in the pathogenesis of FMF is the uncontrolled activation of the pyrin inflammasome and the subsequent release of pro-inflammatory cytokines such as interleukin (IL)-1 β , which contributes substantially to systemic inflammation [3, 89, 90]. It is also described that, beyond FMF, IL-1 β plays a role in neuroinflammation and in various neurological disorders, including multiple sclerosis and autoimmune encephalomyelitis [91, 92]. This cytokine is also produced by microglia and may modulate synaptic activity and blood-brain barrier permeability by promoting a pro-inflammatory environment within the nervous system [91–96]. To date, the role of IL-1 β in migraine remains debatable, whereas stronger evidence supports its involvement in febrile seizures [96–99]. However, although a range of neurological manifestations have been reported in children with FMF, and some observational data suggest a higher prevalence of conditions such as migraine and febrile seizures compared to the general pediatric population, even if somewhat expected given the high number of fever episodes, a direct causal association remains unconfirmed. Therefore, caution is warranted in distinguishing true causal relationships from mere clinical co-occurrences.

Knowledge gaps, limitations and future directions

According to our findings, key knowledge gaps emerged. These include the lack of prospective controlled studies assessing the prevalence and causality of neurological involvement in children with FMF, limited data on *MEFV* genotype correlations, particularly regarding neurological outcomes, and insufficient exploration of underlying pathophysiological mechanisms. To address these gaps, future research should incorporate standardized neurological assessments into both clinical practice and research protocols. Moreover, strengthened collaboration through multicenter prospective cohort studies and international registries aimed at harmonizing data and standardizing neurological assessments is essential to advance our knowledge on the topic.

This study has several limitations. First, some patients were classified as having FMF without specifying the classification criteria used, potentially resulting in a lack of specificity and generalizability of our findings. A major limitation of this review is the absence of disease control groups in the included studies, which limits our ability to attribute the observed prevalence of neurological manifestations specifically to FMF. Therefore, causality cannot be established, and the findings should be interpreted with caution. We excluded non-English articles, which may have led to the omission of relevant data and potentially introduced a geographic and cultural bias, underrepresenting regional differences in neurological

manifestations and reporting practices. Moreover, it is important to consider potential reporting and publication bias, particularly for rare neurological manifestations, which are often described in isolated case reports and may not reflect their broader relevance. In several studies, it has not been possible to examine variables such as the onset age of neurological manifestations, other comorbidities and their *MEFV* genotype, especially in older reports. Lastly, neuropsychiatric and autonomic manifestations such as anxiety, depression, and cardiac rhythm abnormalities were not included in this review, and additional studies are needed to better elucidate these aspects.

Conclusion

Children with FMF may present with a heterogeneous range of neurological manifestations, including more common headaches and seizures and rarer demyelinating disorders, cochlear or vestibular or retinal abnormalities. Febrile seizures and headaches may be more common in children with FMF than in the general pediatric population, particularly in those with poorly controlled disease. However, evidence mostly comes from observational data. A causal relationship has not been established, and a reporting bias cannot be excluded. Clinicians should investigate neurological symptoms in these patients, especially migraines and febrile seizures, as these symptoms may be underreported yet significantly impact quality of life. Multicenter prospective studies employing standardized neurological assessments are essential to better characterize these manifestations and their burden in children with FMF.

Abbreviations

EEG	Electroencephalography
FMF	Familial Mediterranean fever
IgA	(Immunoglobulin A)
IL	Interleukin
MRI	Magnetic resonance imaging
TTH	Tension-type headaches

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Authors' contributions

SLB conceptualized the study. SLB, AC, and DB drafted the manuscript. SLB, ADL, GS, DB, YB and MR performed the literature search and data analysis. MG, SO, GPM and RC contributed to the interpretation of the analyzed data and supervised the study. All authors critically reviewed and had full responsibility for the integrity and accuracy of all aspects of the study.

Artificial intelligence (AI) tools

AI was used for minor grammar and spelling corrections.

Data sharing

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Declarations

Ethical approval and consent to participate

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Competing interests

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