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CASE REPORT

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Solving a diagnostic dilemma in a patient with periodic fever—When the pieces of the puzzle finally fit

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Key Clinical Message

The lack of pediatric subspecialists locally prior to 5 years ago, meant that some of our patients with rare, relapsing conditions were left behind. Familial Mediterranean fever can be diagnosed clinically and supported via genetic panel studies. Although neurological symptoms can be non-specific, this system symptomatology may lead patients and carers to seek medical attention. When neurological symptoms progress, seemingly refractory to first-line treatment, or suggestive of colchicine resistance, CNS demyelination should be considered by the neurologist.

Abstract

Familial Mediterranean fever (FMF) is an inherited disorder with episodic fevers accompanied by pain in the abdomen, joints, or chest. It is a clinical entity that can be confirmed with a specific genetic mutation. Neurological symptoms have not been a focal point in clinical case descriptions. We aim to present the long road to diagnosing our patient, where the diagnostic clues centered around her neurological symptoms.

KEYWORDS

erysipelas-like erythema, familial Mediterranean fever, MEFV, MS overlap, periodic fever

1 | BACKGROUND

The term periodic fever syndrome is defined as three or more episodes of unexplained fever in a 6-month period, occurring at least 7 days apart.[1] Periodic fever syndromes were initially categorized by Mendelian inheritance patterns. They have recently been classified based on immune mechanisms—IL-1v beta activation disorders and protein folding disorders of the innate immune system.[2]

Familial Mediterranean fever (FMF) is the most common inherited periodic auto-inflammatory disease with multiple systemic manifestations.[3]

Diagnostic criteria for familial Mediterranean fever diagnosis are as follows.[4]

A definitive diagnosis is based on two major or one major and two minor criteria.

A probable diagnosis is based on one major and one minor criteria.

Major criteria include:

1. Recurrent febrile episodes of peritonitis, synovitis, or pleuritis
2. Amyloid-associated protein (AA)–type amyloidosis with no predisposing disease
3. Favorable response to continuous colchicine treatment

Minor criteria include:

1. Recurrent febrile episodes
2. Erysipelas-like erythema
3. Familial Mediterranean fever in a first-degree relative

The MEFV gene makes a protein called pyrin. Pyrin plays a role in the natural control of inflammation. Familial Mediterranean fever is associated with either one or two abnormal copies of this gene, thereby leading to episodes of uncontrollable inflammation.[5]

Our case is unique as our patient was worked up for an eventual diagnosis of a genetic auto-inflammatory condition based on her neurological symptomatology. Even though all the clues were present over the past 12 years, this was considered only after other diagnoses were eliminated.

2 | CASE PRESENTATION

KL was first reviewed in the pediatric neurology clinic in November 2021. She was referred by her private pediatrician for assistance with her chronic headaches and probable seizure episodes.

She initially presented at 3 years old with joint pains (knees, ankles) and an associated tender, raised erythematous rash over the affected joints. Rheumatoid factor was positive, and a probable diagnosis of juvenile idiopathic arthritis was considered.

At 11 years old during secondary school examination preparation, she presented to hospital with headaches, alternating weakness involving both sides of her body, intense pain of her fingers and toes, non-specific muscle, and join pains and varying rashes with associated fever (Figure 1 shows palmar rash). She was trialed on prophylactic medication for migraine headaches, including propranolol and topiramate. Gabapentin did not improve her neuropathic pain, and non-steroidal anti-inflammatory drugs (NSAIDs) did not relieve joint or muscle pains.

Three years later at 14 years old, she presented to hospital with first-time seizures during sleep and worsening headaches. The onset of the seizures was not witnessed, and she was found by her mother during the event with stiffening and jerking of all limbs, eyes rolled upward and unresponsive for up to 5 min and slept after.

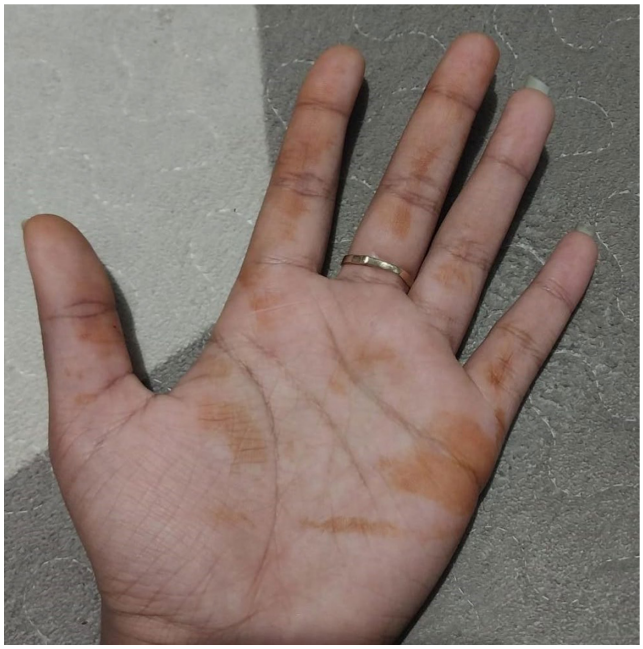

FIGURE 1 Post-flare; these areas would be hot, swollen, tender, and erythematous during a flare.

She was assessed at her pediatric district hospital and diagnosed with functional neurological disorder. Both the patient and her mother were not happy with this assessment as blood and electroclinical investigations were reported as abnormal. Her private pediatrician agreed that this was not an underlying psychological condition. Therefore, her evaluation was escalated to involve various pediatric subspecialists.

On review of the history, she had been experiencing behavior arrest events with associated lip smacking and fiddling with her clothes, lasting for several minutes, where she would be partially responsive, and drowsy after. These occurred prior to the tonic–clonic seizure.

She was investigated for an undifferentiated connective tissue disorder and secondary CNS vasculitis or vasculopathy. Interestingly, her blood pressure readings were also found to be borderline for her age and height, and she had persistent proteinuria. A renal biopsy was performed to exclude a vasculitic condition.

At 15 years old, she was hospitalized for a cluster of focal motor tonic–clonic seizures occurring during sleep. This was associated with a documented fever and a raised, urticarial rash over her back that resolved within 4 h. During this hospitalization, her inflammatory markers were repeated (blood and CSF).

In addition, over the past 4 years, she experienced the following symptoms:

- A history of photosensitive rash over her face, dermatographia, oral ulcers, Raynaud's phenomenon.
- Headaches that were worse in the morning, over temporal location, no relief with analgesia, and associated blurry vision, periods of insomnia, and memory loss.
- Early morning puffiness around eyes.

3 | INVESTIGATIONS

1. Thrombocytosis (platelet count >500,000), elevated ESR (38 mm/h during one minor flare), Rouleaux formation blood film, DCT negative
2. Anticardiolipin Ab IgG 102.4 (neg <14) IgM 24.6 (neg <14), ANA titer 1:100; pattern – cytoplasm smooth to fine granular + ENA screen anti-Mi-2B +; ANCA studies normal (MPO, PR3 antibodies not done), normal complement levels, CK 170 (UL normal)
3. CSF protein 39 mg/dL (UL normal), three white cells (not accounted for by RBC 12); Paired OCB—1 band CSF (0 blood)
4. EEG ×2 at 14 years and 15 years old: sharp waves and focal slowing over the temporal regions (maximal posterior/right-sided); MRI/MRA/MRV at 15 years old was unremarkable
5. Renal biopsy at 15 years old—No features of ANCA-associated RPGN or thrombotic microangiopathy

4 | TREATMENT

She was started on carbamazepine 200/400 mg bd (8 mg/kg/day) and was counseled on the risk of medication overuse headaches. Hydroxychloroquine 200 mg twice daily was started by the rheumatology team and showed a positive effect.

5 | OUTCOME AND FOLLOW-UP

On review of her clinical summary, investigations and case reviews, the team strongly considered a diagnosis of periodic fever syndrome.

The Invitae genetic auto-inflammatory panel (periodic fever syndromes) was performed:

1. Pathogenic variant, c.2230G>T (p.Ala744Ser), was identified in MEFV (MedGen UID: 341987, PMID: 23844200).
2. Variant of uncertain significance, c.411C>A (p.Phe137Leu), was identified in NLRP12 (MedGen UID 435869, ClinVar ID1971429).

She started colchicine, with a general improvement in her neurological symptoms and flare-ups. However, she is not yet completely controlled. Tocilizumab (IL-6 receptor blocker) is being considered as a treatment adjunct due to her minimal response to methotrexate.

6 | DISCUSSION

Trinidad and Tobago has a mixed ethnic population, however, comprises of two main groups by descent—East Indians and Africans. The main systemic autoimmune condition diagnosed locally is systemic lupus erythematous (SLE). Therefore, the diagnosis of a periodic fever syndrome is historically not highly considered in our pediatric patients.

In Trinidad and Tobago, the use of genetics studies has also not been our strong suit. This is mainly due to its unavailability in the public healthcare setting as well as the costs associated. However, with the recent availability of genetic testing panels at a reasonable cost privately (approximately 350 GBP total), clinicians have been recommending this service to assist in difficult diagnoses, tailor treatment, and counsel appropriately on outcomes.

Familial Mediterranean fever is usually inherited in an autosomal recessive manner. However, autosomal dominant inheritance has been reported in individuals with pathogenic variants, albeit at a lesser clinical severity. An increased frequency of MEFV pathogenic variants have also been reported in individuals with genetically related diseases like Behçet, ulcerative colitis, and juvenile idiopathic arthritis.[6] Finally, it has been suggested that people with a single MEFV pathogenic variant with signs of disease may have other low penetrance genetic risk factors increasing inflammation—in this patient, a variant of uncertain significance was additionally found in the NLRP12 gene, associated with autosomal dominant familial cold auto-inflammatory syndrome. This may be a possible mechanism of this last hypothesis.

This patient had one major criteria (recurrent febrile episodes of synovitis) and two minor criteria (recurrent febrile episodes and erysipelas-like erythema) for a diagnosis of FMF. Even though her most worrisome symptoms were neurological, this was preceded by a long history of intermittent fever with associated rash and joint pains. During flares, her ESR results were elevated, there was a reactive thrombocytosis and notable Rouleaux formation. Anticardiolipin antibodies were significantly elevated, but her ANA and ENA results were weakly positive. Altogether, this lent to an underlying inflammatory etiology. However, due to the lack of subspecialty services locally when the patient initially presented in childhood, this possibility was not pursued.

The single oligoclonal band in her CSF was not discounted. It is possible that, as her clinical picture evolves, a second co-occurring diagnosis could be made. This would certainly be considered if colchicine resistance develops.

Akman Demir et al[7] found 12 FMF patients (9 with MS and 3 with non-MS demyelinating diseases) by evaluating 2800 MS patients. They suggested a four-fold increased rate of FMF among patients with MS and reported that the presence of MEFV variations could change the incidence and progression of other inflammatory diseases. A separate analysis of a Turkish cohort of MS patients with a MEFV mutation, regardless of subtype, progressed to a more advanced disease course sooner, and also had a higher annual relapse rate than matched controls without MEFV mutations cohort.[8] However, additional studies are needed to elucidate whether any potential influence of MEFV mutation on MS disease course exists as contrasting studies[9,10] have not found any influence.

The use of various disease-modifying agents is reported in the literature for the treatment of FMF-MS. However, a best practice approach has not yet been determined. IL-1 targeting therapy (anakinra or canakinumab) has been successful in managing both overlap conditions in two case reports, while a third report described relapse freedom on colchicine and rituximab using clinical and MRI follow-up data.[11–13] A case series of ocrelizumab treatment for 18 months in 11 people with secondary progressive MS showed reduction in both FMF and MS attacks.[14]

The ultimate goal of treatment in FMF is to obtain complete control of unprovoked attacks and minimize subclinical inflammation in between attacks.[15]

Using the available clinical case reports published thus far, and balancing the availability of agents locally, the treatment approach tailored for our patient (with close monitoring for FMF-MS overlap) would include tocilizumab, and if unsuccessful, ocrelizumab.

AUTHOR CONTRIBUTIONS

Vanita Shukla: Conceptualization; writing – original draft; writing – review and editing. **Virendra R. S. Sarabjit Singh:** Project administration; supervision; writing – review and editing. **Cara Ranghell:** Investigation; writing – original draft. **Celine Ramgoolam:** Data curation; writing – original draft. **Nicole S. Solomon:** Conceptualization; investigation; visualization. **Vidya Ramcharitar-Maharaj:** Conceptualization; investigation; visualization. **Christophe Persad:** Investigation; writing – review and editing. **Keisha Davis-King:** Investigation; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DECLARATION STATEMENT

I, Vanita Shukla, the author has the right to grant and does grant on behalf of all authors, an exclusive license and/or a non-exclusive license for contributions from authors to permit this Work (as institutional ethical approval has been granted), if accepted, to be published.

CONSENT

Written informed consent was obtained from the patient and parent/guardian to publish this report in accordance with the journal's patient consent policy.

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REFERENCES

1. Firestein and Kelly. *Hereditary Periodic Fever Syndrome*. 9th online ed. Kelly's Textbook of Rheumatology. 2017.
2. McDermott MF, Aksentijevich I. The autoinflammatory syndromes. *Curr Opin Allergy Clin Immunol*. 2002;2(6):511-516.
3. Ahmed MH, Ibrahim AM, Ragab SM, Mahros AM. Musculoskeletal and neurological manifestations in a cohort of Egyptian familial Mediterranean fever patients: genotype-phenotype correlation. *Egypt Rheumatol Rehabil*. 2022;49:6. doi:10.1186/s43166-021-00106-w
4. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum*. 1997;40(10):1879-1885.
5. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Familial-Mediterranean-Fever#:~:text=Familial%20Mediterranean%20Fever%20(FMF)%20is%20a%20genetic%20disorder%20that%20causes,episodes%20typically%20begin%20in%20childhood
6. Shohat M. Familial Mediterranean fever. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. University of Washington; 2000. https://www.ncbi.nlm.nih.gov/books/NBK1227/
7. Sayin R, Alpayci M, Soyoral YU. A case with multiple sclerosis and familial Mediterranean fever. *Genet Couns*. 2011;22:309-312.
8. Akman-Demir G, Gul A, Gurol E, et al. Inflammatory/demyelinating central nervous system involvement in

familial Mediterranean fever (FMF): coincidence or association. *J Neurol*. 2006;253:928-934.
9. Unal A, Dursun A, Emre U, Tascilar NF, Ankarali H. Evaluation of common mutations in the Mediterranean fever gene in multiple sclerosis patients: is it a susceptibility gene? *J Neurol Sci*. 2010;294(1):38-42. doi:10.1016/j.jns.2010.04.008
10. Terzi M, Taskın E, Unal Akdemir N, Bagcı H, Onar M. The relationship between familial Mediterranean fever gene (MEFV) mutations and clinical and radiologic parameters in multiple sclerosis patients. *Int J Neurosci*. 2015;125(2):116-122. doi:10.3109/00207454.2014.913170
11. Ozdogan H, Ugurlu S, Uygunoglu U, et al. The efficacy of anti- IL-1 treatment in three patients with coexisting familial Mediterranean fever and multiple sclerosis. *Mult Scler Relat Disord*. 2020;45:102332. doi:10.1016/j.msard.2020.102332
12. Öztürk B. Familial Mediterranean fever and multiple sclerosis successfully treated with interferon Beta-1a: a case report. *Arch Rheumatol*. 2019;34(4):443-446. doi:10.5606/ArchRheumatol.2019.7249
13. Pozzato M, Micaglio E, Starvaggi Cucuzza C, et al. Case report: efficacy of rituximab in a patient with familial Mediterranean fever and multiple sclerosis. *Front Neurol*. 2021;11:591395. doi:10.3389/fneur.2020.591395
14. Demir CF, Balgetir F, Ethemoglu O, et al. Positive effects of ocrelizumab in patients with familial Mediterranean fever and coexistent multiple sclerosis. *Arch Rheumatol*. 2021;36(2):219-226. doi:10.46497/ArchRheumatol.2021.8229
15. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. *Ann Rheum Dis*. 2016;75:644-651.

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