Marshall syndrome in a young child, a reality

Case report

Laura Mihaela Trandafir, MD, PhD; Madalina Ionela Chiriac, MD; Smaranda Diaconescu, PhD, MD; *Ileana Ioniuc, MD, PhD; Ingrith Miron, PhD, MD; Daniel Rusu, MD

Abstract

Background: Recurrent fever syndrome, known as the Marshall syndrome (MS), is a clinical entity that includes several clinical features, such as: fever (39–40°C) that occurs repeatedly at variable intervals (3–8 weeks) and in episodes of 3 to 6 days, cervical adenopathy, pharyngitis, and aphthous stomatitis. The diagnosis of MS is one of exclusions; laboratory data is nonspecific and no abnormalities correlated with MS have been detected thus far.

Methods: The authors report the case of a 2-year-old girl admitted to a tertiary pediatric center for repeated episodes of fever with aphthous stomatitis and laterocervical adenopathy.

Results: The child’s case history raised the suspicion of MS, which was subsequently confirmed by exclusion of all the other differential diagnoses (recurrent tonsillitis, juvenile idiopathic arthritis, Behçet’s disease, cyclic neutropenia, hypergloobulinemia D syndrome). After the 3 febrile episodes, bilateral tonsillectomy was performed based on the parents’ consent, with favorable immediate and remote postoperative clinical outcomes. The diagnosis of MS is one based on exclusion, as laboratory data is nonspecific. We took into consideration other causes of recurrent fever (recurrent tonsillitis, infectious diseases, juvenile idiopathic arthritis, Behçet’s disease, cyclic neutropenia, Familial Mediterranean fever syndrome, hypergloobulinemia D syndrome). In our case, MS criteria were met through clinical examination and the child’s outcome. Subsequently, laboratory data helped us establish the MS diagnosis.

Conclusions: Pediatricians should consider the MS diagnosis in the context of recurrent fever episodes associated with at least one of the following symptoms: pharyngitis, cervical adenopathy or aphthous stomatitis. Despite the indication for tonsillectomy in young children being controversial, in this case the surgery led to the total remission of the disease.

Abbreviations: AIM2 = absent in melanoma, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CASP1 = caspase 1, apoptosis-related cysteine peptidase, CMV = cytomegalic virus, EBV = Epstein–Barr virus, H = height, Hb = hemoglobin, HR = heart rate, Ht = hematocrit, IFN = interferon, Ig = immunoglobulin, IgAN = IgA nephropathy, IL = interleukins, M = monocytes, MEFV = Mediterranean fever, MS = Marshall syndrome, NSAIDs = nonsteroidal anti-inflammatory drugs, PLT = platelet, TNF = tumor necrosis factor, W = weight, WBC = white blood cells.

Keywords: child, Marshall syndrome, recurrent fever

1. Introduction

Marshall syndrome (MS) was described for the first time by Dr. Gary Marshall in 1987. In 1989, MS was defined as recurrent fever associated with pharyngitis, cervical adenopathy, and aphthous stomatitis (Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis—PFAPA). These symptoms occur at 3 to 8 weeks’ intervals and sometimes, may be associated with white tonsillar deposits. In the febrile episodes, the patients have leukocytosis and increased acute phase reactants, while the infectious etiology remains unproven.
The MS diagnosis is an exclusion one, although laboratory data is nonspecific, and, until now, specific abnormalities for MS were not reported in the literature.[4]

2. Case presentation

A 2-year-old girl was admitted into our service for impaired general health condition, hyperthermia, dysphagia, and anorexia. The onset was 2 days prior to admission, presenting hyperthermia (39.5°C) associated with anorexia and dysphagia. The child’s mother administered antipyretic drugs (acetaminophen and ibuprofen), without remission of fever (after 24 hours), that had led to progressive worsening of the patient’s general state.

Medical history revealed that the child had 2 febrile episodes within the last 2 months, treated successfully with antipyretics that led to complete recovery in <24 hours. In this context, the parents called upon our unit for further investigations.

Previous medical history revealed 6 episodes of upper respiratory tract infections, spanning over a period between 14 and 20 months.

Physical examination upon admission showed the following aspects: affected general condition, no loss of consciousness, fever (39.3°C), W = 14 kg, H = 90 cm, paleness, normal subcutaneous tissue, bilateral lateral-cervical adenopathy <5 mm, mobile and painless; rhythmic heart sounds, HR = 130 bpm (in feverish conditions), hyperemic pharynx, aphthous stomatitis, and hypertrophic, congestive tonsils with bilateral pus deposits.

Laboratory data indicated leukocytosis, anemia, inflammatory syndrome, low serum iron, and negative EBV antibodies. The child was treated with intravenous antibiotic (the total dose calculated for the child’s weight was 1,000,000 IU penicillin, divided in 4 doses/day) for 5 days and antipyretics (acetaminophen 40 mg/kg/day, divided in 4 doses and ibuprofen 20 mg/kg/day, divided in 3 doses) for 3 days long. The fever stopped after 3 days and the girl was dismissed after 3 days of hospitalization.

Three weeks later (second admission) the patient returned to our clinic with high fever (39.5°C). Physical examination revealed once again a hyperemic pharynx with hypertrophic and congested tonsils, aphthous stomatitis, and submandibular adenitis.

Laboratory findings indicated leukocytosis, monocytes, anemia, and thrombocytosis. The pharyngeal swab was negative. The patient was treated with an intravenous antibiotic (1,000,000 IU penicillin, divided in 4 doses /day) for 5 days long and antipyretic drug (acetaminophen 40 mg/kg/day, divided in 4 doses) for 3 days long. For the second time, the fever stopped after 3 days.

After another 3 weeks (third admission), the child had the same symptomatology.

Laboratory data showed: leukocytosis, inflammatory syndrome, mild anemia, low serum iron, normal value of liver tests, normal levels of serum immunoglobulin; CMV Ig M and Ig G antibodies and toxoplasma IgM antibodies were negative. The antinuclear antibodies and rheumatoid factor were negative.

Moreover, the throat swab culture and blood cultures after 48 hours and 7 days of incubation were negative.

Malignant hematological disease (acute lymphoblastic leukemia) was suspected. Once the hematologist performed a spinal puncture, the presence of normal bone marrow cells excluded this diagnosis.

Laboratory data and their dynamic evolution are presented in Table 1.

Considering the diagnostic criteria (recurrent fever, aphthous stomatitis, pharyngitis, cervical lymphadenopathy), we presumed the patient had MS, therefore beginning treatment with dexamethasone (0.2 mg/kg/b.i.d., administered intravenously), which led to a prompt relief of the fever within 4 hours. Due to technical reasons (lack of kits from the hospital) pro-inflammatory cytokines were not tested.

Tonsillectomy was taken into consideration as a curative treatment. After complete remission of the third febrile episode,
3. Discussions

In a retrospective study reported by the incidence of MS was 0.4 cases/1000 children/year, with 1 new diagnosed case of MS per pediatrician every 1 or 2 years. Another study carried out by Grvoll et al\(^{[6]}\) reported that the incidence of MS in Norway was 2.3/10,000 in children up to 5 years of age.

MS was included in the category of autoinflammatory syndromes. This term was introduced by Kastner for all those disorders that are not in the classical groups of immune-mediated diseases. This group of immune-mediated diseases is characterized by recurrent febrile episodes associated with rheumatologic symptoms involving the joints, muscle tissue, skin, and eyes.\(^{[2]}\) Auto-inflammatory syndromes are associated with the disruption of the innate immune response and subsequent, consecutive episodes of spontaneous acute inflammation.\(^{[8,9]}\)

Diagnostic criteria for MS are presented in Table 2.\(^{[9,10]}\)

The etiology of MS is unknown, but prompt response after a single dose of corticosteroid seems to be caused rather by permanent production of inflammatory cytokines than by an infectious process. Studies on cytokines' dynamics showed a rapid rate of rise and fall of pro-inflammatory cytokines (IL-1β, IL-18, TNF-α, and IFN-γ) at the onset. Also was observed an increased IL-6 level in case of high fever or chills, with normalization in periods without fever. T lymphocytes associated IL-7, IL-17, and anti-inflammatory cytokines (IL-10 and IL-4) decrease during febrile episodes. IL-1β plays an important role in all autoinflammatory responses, including MS. Recent studies claim that the production of IL-1β by monocytes is constant in patients with MS, as a result of altered inflammasome activation, probably related to genetic defects of inflammasome. In patients with MS, the increase of inflammasome associated genes (AIM2, CAPS1) and expression of IL-1 occur during febrile episodes. Moreover, there were reports regarding the therapeutic efficacy of IL-1β blockade with flare remission. All these mutations are involved in the pathogenesis associated with MS.\(^{[10]}\)

In 2014, Salehzadeh et al\(^{[11]}\) carried out a study that assessed the most common MEFV gene mutations in 12 patients with MS. Only 30% of patients had mutations of this gene, but further studies are required for confirmation.

The MS diagnosis is one of exclusions; laboratory data are nonspecific and thus far no abnormalities correlated with MS were detected.\(^{[11]}\)

Thus, it is important to eliminate other cases of recurrent fever such as recurrent tonsillitis, infectious diseases, juvenile idiopathic arthritis, Behçet’s disease, cyclic neutropenia, Familial Mediterranean fever syndrome, hyperglobulinemia D syndrome.\(^{[1–4]}\) Some infectious diseases such as the ones mentioned before are accompanied by febrile episodes and periods without fever, but in their case the diagnosis can be confirmed using laboratory methods.\(^{[2,11]}\)

Juvenile idiopathic arthritis is characterized by the occurrence of arthritis, fever, generalized lymphadenopathy, and hepatosplenomegaly. Patients experience morning stiffness, rash, and uveitis, with positive rheumatoid factor and antinuclear antibodies.\(^{[12,13]}\)

In our case, the child only had fever and local lymphadenectomy, and laboratory data showed negative rheumatoid factor and antinuclear antibodies.

Behçet’s disease presents oral aphthous ulcers, genital ulcerations, iridocyclitis, and synovitis.\(^{[14]}\) Our patient only had aphthous stomatitis, without oral ulcers, iridocyclitis or synovitis, that occur in Behçet’s disease.

Cyclic neutropenia usually has its onset in the first year of life, presenting low levels of neutrophils that can go down all the way to zero, in episodes that recur every 3 weeks. During the episodes, children develop mucositis, otitis, and skin infections.\(^{[4,9]}\) In our case, the child was 2 years old and she had neutrophilia associated with the inflammatory syndrome, with no past medical history of repeated episodes with neutropenia in the first years of life. Hyperglobulinemia D syndrome is characterized by the variable length and occurrence intervals of febrile episodes associated with headache, cervical lymphadenopathy, arthritis, mucular rash, and splenomegaly. Laboratory investigations indicate elevated Ig D serum level; during the febrile attack, the urinary mevalonic acid output is increased.\(^{[5,9]}\)

In our case, the child had fever and cervical lymphadenectomy without arthritis, mucular rash and splenomegaly; laboratory data also revealed normal levels of Ig D and other serum immunoglobulins.

Familial Mediterranean fever syndrome is clinically similar to MS, but patients have a positive family history, and are unresponsive to corticosteroids, whereas colchicine is the therapeutic option.\(^{[13]}\) Our patient had no positive family history of fever syndrome and was responsive to the administration of corticosteroids.

Antibiotics and NSAIDs are ineffective in MS which promptly respond to a single dose of prednisolone or betamethasone. These are part of the first-line therapy and lead to prolonged remissions, but do not prevent any subsequent febrile episodes. The fever disappears within 2 to 4 hours, but the aphthous stomatitis can persist for several days. Cimetidine is used for fever prevention in some centers.\(^{[4,8]}\)

Recent data showed that tonsillectomy with or without resection of adenoids leads to symptom remission in over 90% of cases, but consensus is yet to be reached in terms of its therapeutic recommendation.\(^{[8]}\)

There is literature presenting the association of IgA nephropathy (IgAN) and MS in a 10-year-old boy. Tonsillectomy was subsequently performed, leading to the remission of MS and improvement of clinical outcome in terms of IgAN.\(^{[16]}\)

---

### Table 2

Diagnostic criteria for MS.\(^{[8,10]}\)

| Recurrent fever in a child | ≤ 5 years |
|---------------------------|----------|
| One or more of the following symptoms, aside from upper respiratory tract infections: |
| • Aphthous stomatitis |
| • Pharyngitis |
| • Cervical lymphadenopathy |
| Exclusion of cyclic neutropenia in intervals, whereas the child is afebrile, asymptomatic, with normal growth and development rates. |

MS = Marshall syndrome.
In our opinion, in countries in top position with respect to the frequency of nonprescription use of antimicrobials in the general population, the diagnosis of MS should be evoked in order to avoid unnecessary antibiotic treatments.

The particularities of the case consisted in the difficulty to establish the diagnosis, and recognizing the importance of parents addressing the same pediatrician in case of recurring symptoms. Furthermore, tonsillectomy was the curative treatment for MS, in spite of the controversial opinions on performing such surgery in young children. Episodes may affect the quality of life of both children and their families through school absenteeism.

The prognosis for this condition is favorable, and children diagnosed with MS have normal development. There were no reported morbidity or mortality associated with MS.[14,17]

4. Conclusions

Pediatricians should consider the MS diagnosis in the context of recurrent fever episodes in children under the age of 5, at intervals of 3 to 8 weeks, lasting for 3 to 6 days and associated with at least one of the following symptoms: pharyngitis, cervical adenopathy or aphthous stomatitis. There is no specific laboratory test for MS. In spite of its controversial indication in young children, bilateral tonsillectomy was performed and determined favorable clinical and biological outcomes.

Acknowledgments

The authors extend their heartfelt thanks to the Pediatric Department staff from “Sfanta Maria” Clinical Emergency Hospital for Children, Iasi, Romania

References

[1] Berlucchi M, Nicolai P, Marshall’s syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome. Orphanet Encyclopedia 2004;1–5. https://www.orpha.net/data/patho/GB/uk-PFAPA.pdf
[2] Berlucchi M, Meine A, Plehani A, et al. Update on treatment of Marshall’s syndrome (PFAPA syndrome): report of five cases with review of the literature. Ann Otol Rhinol Laryngol 2003;112:365–9.
[3] Tasher D, Somekh E, Dalal J. PFAPA syndrome: clinical aspects the new disclosed. Arch Dis Child 2006;91:981–4.
[4] Ahmadinejad Z, Mansori S, Ziaee V, et al. Periodic fever: a review on clinical, management and guideline for Iranian patients—Part I. Iran J Pediatr 2014;24:1–3.
[5] Cattalini M, Solizani M, Rigante D. Basic characteristics of adults with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome in comparison with the typical pediatric expression of disease. Mediators Inflamm 2015;2015:570418.
[6] Forsvoll J, Kristoffersen EK, Øymar K. Incidence, clinical characteristics and outcome in Norwegian children with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome; a population-based study. Acta Paediatr 2013;102:187–92. doi: 10.1111/apa.12069. Epub 2012 Nov 27.
[7] Kasmer DL. Hereditary periodic fever syndromes. Hematology Am Soc Hematol Educ Program 2005;74–81. doi: 10.1182/asheducation-2005.1.74.
[8] Stojanov S, Lapidus S, Chirkara P, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA): a disorder of Innate Immunity and Th1 activation responsive to IL-1 blockade. Proc Natl Acad Sci U S A 2011;108:7148–53.
[9] De Sanctis S, Nozzle M, Del Torto M, et al. Autoinflammatory syndromes: diagnosis and management. Ital J Pediatr 2010;36:57.
[10] Perko D, Debeljak M, Toplak N, et al. Clinical features and genetic background periodic fever syndrome of the aphthous stomatitis with, pharyngitis, and adenitis: a single center longitudinal study of 81 patients. Mediators Inflamm 2015;2015:293417.
[11] Salehzadeh F, Vahedi M, Hosseini S, et al. PFAPA and gene mutations 12 common MEFV our clinical experience. Iran J Pediatr 2014;24:64–8.
[12] Mehrregan FF, Ziaee V, Ahmadinejad Z, et al. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) Iranian syndrome in children; first report of Iranian periodic fever and autoinflammatory registry (IPFAIR). Iran J Pediatr 2014;24:598–602.
[13] Oberle EJ, Harris JG, Verbsky JW. Polyarticular juvenile idiopathic arthritis—epidemiology and management approaches. Clin Epidemiol 2014;6:379–93.
[14] Saleh Z, Arayssi T. Update on the therapy of Behçet disease. Ther Adv Chronic Dis 2014;5:112–34.
[15] Ben-Zvi I, Herskovizh C, Kukuy O, et al. Familial Mediterranean fever without MEFV mutations: a case-control study. Orphanet J Rare Dis 2015;10:34.
[16] Sugimoto K, Fujita S, Miyazawa T, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome IgA nephropathy and. Pediatr Nephrol 2013;28:151–4.
[17] Esposito S, Bianchini S, Fattizzo M, et al. The enigma of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome. Pediatr Infect Dis J 2014;33:650–2.