

## Case Report

**A RARE CASE OF A SEVERE COURSE OF SYSTEMIC ONSET OF JUVENILE IDIOPATHIC ARTHRITIS ASSOCIATED WITH *MEFV* GENE MUTATIONS IN A 12-YEAR-OLD GIRL**Svitlana Ilchenko<sup>1</sup>, Anastasiia Fialkovska<sup>1</sup>, Svitlana Ivanus<sup>2</sup>, Tetiana Baraley<sup>2</sup>**Author information:** <sup>1</sup> Dnipro State Medical University, Department of Propedeutics of Pediatric Diseases, Dnipro, Ukraine, <sup>2</sup> Dnipro City Children's Clinical Hospital № 6, Dnipro, Ukraine.

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**Abstract:** Juvenile idiopathic arthritis (JIA) is a common rheumatic disease in children and adolescents. *MEFV* (Mediterranean fever, FMF) gene mutations are observed in systemic-onset JIA, that in addition to increasing the risk of JIA development, worsen the disease prognosis. We reported a rare case of a severe systemic-onset JIA associated with *MEFV* gene mutations in a 12-year-old girl. The patient had an aggressive disease course and resistance to conventional immunosuppressive agents. This case confirms the difficulties of diagnostic and treatment of systemic JIA (sJIA) associated with FMF. Currently, there are no established criteria for the definition or differential diagnosis of arthritis associated with FMF. The severe prognosis of JIA associated with FMF should motivate clinicians to initiate aggressive therapy early.

**Keywords:** Juvenile idiopathic arthritis, Familial Mediterranean Fever, Children.

**INTRODUCTION** Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and a leading cause of short- and long-term disability [1]. JIA is a heterogeneous group of conditions that encompasses all forms of arthritis of unknown etiology lasting for at least six weeks and with onset before 16 years old. As a result of the lack of pathognomonic features, the diagnosis of JIA is one of exclusion among all possible causes of chronic arthritis in childhood. It has various clinical features like systemic arthritis, oligoarthritis, rheumatoid factor positive and negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated forms [2]. The reports on incidence rates of JIA differ depending on the study design and geographic region. The incidence rates of JIA differ between 15.0/100,000/year in the Nordic countries [3], 10.3/100,000 in Minnesota (USA) [4], 8.5/100,000 in Manitoba (Canada) [5], 6.9/100,000 in Catalonia (Spain) [6] and 3.1/100,000 in Alsace (France) [7].

Systemic juvenile idiopathic arthritis accounts for 5–15 % of children with JIA in North America and Europe [8]. The ILAR criteria for systemic arthritis require the presence of arthritis accompanied or preceded by a documented quotidian fever of at least two weeks' duration, plus at least one of the following:

- Characteristic rash
- Generalized symmetrical lymphadenopathy
- Enlargement of liver or spleen
- Serositis (pericarditis, pleural or pericardial effusion, rarely peritonitis)

The fever has a typical intermittent pattern, with one or two daily spikes, up to 39°C or higher, followed by a rapid return to baseline. The erythematous, salmon pink, evanescent macular rash usually appears with fever. Arthritis is often symmetrical and polyarticular but may be absent at onset and develop much later. In these cases, diagnosis cannot be considered definite until arthritis is present [9].

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Cytokine dysregulation plays an important role in the pathogenesis of sJIA. While interferon  $\gamma$  levels are decreased, proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-

8, monocyte chemoattractant protein-1, E-selectin, and intracellular adhesion molecules levels are elevated in sJIA. Recently, the role of interleukin-1 $\beta$  (IL-1 $\beta$ ) in sJIA received attention. Excess IL-1 $\beta$  can result in fever, anorexia, pain hypersensitivity, joint destruction, vasculitis, and thrombosis; its dysregulation can lead to the clinical and laboratory findings of sJIA. IL-1 $\beta$  may be responsible for the elevation in IL-6 which has an important role in affecting the systemic manifestations as well as arthritis in sJIA. Elevation of IL-6 in both peripheral blood and synovial fluid is seen; its expression correlates with disease activity and parallels the fever curve. IL-6 stimulates acute phase reactants [such as C-reactive protein (CRP), serum amyloid A, fibrinogen, and ferritin]. It appears to be responsible for the anemia seen in sJIA and promotes the production of hepcidin. Hepcidin is produced by the liver and is responsible for transmembrane iron transport; when elevated, it prevents the release of iron from the macrophages, hepatocytes, and enterocytes to the plasma, thus causing a decrease in serum iron levels. In addition, IL-6 may activate osteoclasts and cause osteoporosis, as well as instigate cartilage damage [10].

Many previous studies have revealed that common heterozygous or homozygous mutations in the marenostin-encoding fever (*MEFV*) gene are associated with sJIA [11–13]. *MEFV* gene encodes a protein named pyrin or marenostin, which is expressed in neutrophils and monocytes. Pyrin inhibits the processing of the IL-1 $\beta$  to an active form and nuclear factor- $\kappa$ B activation. In the presence of *MEFV* mutations, these actions of pyrin are deficient, and there is uncontrolled production of active IL-1 $\beta$ . This ongoing inflammation leads to recurrent febrile, inflammatory episodes, and appearance of the classical clinical features of Familial Mediterranean Fever (FMF), which is an autosomal recessive disorder [11].

FMF is prevalent among eastern Mediterranean region inhabitants, mainly in non-Ashkenazi Jews, Armenians, Turks, and Arabs [14]. Clinical manifestations appear early in most patients, usually before the age of 10 [15]. The clinical findings include recurrent attacks of peritonitis, pleuritis, pericarditis, synovitis, febrile myalgia, or erysipelas-like erythema associated with fever pain in the abdomen, chest, joints, and muscles. Musculoskeletal involvement in FMF occurs in 70–75% of patients as acute attacks of mono- or oligoarthritis predominantly involving the large joints of the lower extremities with spontaneous resolution within 1 to 3 days; however, it may prolong up

to 1 month or rarely longer, although less than 10% of FMF patients develop protracted arthritis and joint damage leading to disability, especially in the hips or knees [16]. The coexistence of FMF with JIA is a very rare condition with a poor prognosis. Here, we report a case of a severe course of systemic juvenile idiopathic arthritis associated with *MEFV* gene mutations.

**CASE PRESENTATION** A 12-year-old female patient with JIA and FMF has been followed up for ten years in our rheumatology clinic. She was born in Ukraine. Her early development was normal, and she was given all her immunizations on time. She was diagnosed with sJIA when she was two years old. Her first symptoms were fever, maculopapular rashes on the neck, the inguinal folds, the back of the hands, and pain in her hip joints. She was treated with non-steroidal anti-inflammatory drugs and physiotherapy with some improvement. After two months of her initial symptoms, she experienced swelling and morning stiffness in both knee joints and left ankle. One month later, there was swelling in the interphalangeal joints of both hands with severe pain and limited motion. Family medical history was significant for great-grandmother on her mother's side had rheumatoid arthritis.

Laboratory results showed an elevation in inflammatory markers; C-reactive protein (CRP – 192 mg/L), erythrocyte sedimentation rate (ESR – 58 mm/hr), white blood cells (WBC –  $17.0 \times 10^3/\mu\text{L}$ ) and platelets (796.000 platelets/mm<sup>3</sup>), reduction in hemoglobin (Hb – 8,5 g/dL). Rheumatoid factor (RF), anti-nuclear antibody (ANA), and anti-cyclic citrullinated peptide (anti-CCP) were negative.

The systemic-onset JIA with seronegative (rheumatoid factor and ANA) polyarthritis without uveitis was diagnosed in December 2010. Treatment included three pulses of methylprednisolone, 20 mg/kg each, followed by oral methylprednisolone 1 mg/kg for two months with a slow tapering down of the dose. She was also given intravenous immunoglobulin in January 2011. Methotrexate (MTX) was added in March 2011 at a dose of 5 mg once weekly. In November 2011, when the patient was three years old, her weight was 11 kg (below 3rd percentile), and her height was 90 cm (3rd percentile). Both weight and height had decreased from the 50th percentile during her illness. Joint examination showed remarkable synovial swelling of wrists, proximal interphalangeal (PIP), and metacarpophalangeal (MCP) joints, elbows, knees, and ankles with flexion contractures of knees and elbows. Laboratory findings again showed

increased ESR, WBC, and CRP levels and decreased Hb level.

Due to lack of improvement, methylprednisolone dose was increased to 10 mg/day, MTX was increased to 7.5 mg intramuscularly once weekly, and she was started on Etanercept 0.8 mg/kg once weekly. She continued to take folic acid, calcium, and vitamin D.

In 2012, the parents refused medical management, and the patient did not receive any treatment for three years, except for non-steroidal anti-inflammatory drugs for severe joint pain. In May 2013, the child was hospitalized in the rheumatology department with an exacerbation of the joint disease: new joints were involved in the process, and changes in previously affected joints has increased. She had morning stiffness for more than 3 hours and severe fatigue; her gait changed. Objective examination revealed synovitis of the shoulders, elbows, wrists, interphalangeal (Figure 1), hips, knees (Figure 2), ankles (Figure 3), and cervical spine with the formation of contractures in them. Treatment with methylprednisolone and MTX was renewed, but the parents again refused therapy. In May 2015, the girl had almost all small and large joints inflamed, growth retardation, and malnutrition.



Figure 1. The swelling in interphalangeal joints.

The child was periodically febrile, which was accompanied by maculopapular rashes on the skin. She had severe pain in her hips and knees, and the father brought the child in his arms. X-rays of the joints showed diffuse osteoporosis and narrowing of the joint spaces. Biological therapy was started with Tocilizumab (humanized monoclonal antibody against IL-6) 12mg/kg; parents refused again to initiate MTX. During the next year, the child's condition has



Figure 2. The swelling in both knee joints.



Figure 3. The swelling in both ankle joints.

been stabilized. In 2016 she had frequent upper respiratory infections; she also had bronchitis and exacerbations of chronic tonsillitis. Because of that, the intervals between the injections of the Tocilizumab began to increase, and the girl's body temperature began to rise again, and a rash appeared.

In September 2017, treatment with Anakinra (IL-1 receptor antagonist) 50 mg per day subcutaneously was initiated due to the insufficient effect of Tocilizumab. But one month later, after Anakinra initiation, a new episode of arthritis exacerbation occurred. Ultrasound examination showed signs of synovitis, bursitis, tenosynovitis in all joints. In October 2017, Anakinra was changed to Adalimumab (anti-TNF humanized monoclonal

antibody) 20 mg subcutaneously once every 2 weeks. Over the next three months, the patient's condition improved slightly: pain and morning stiffness in the joints decreased, the child began to walk independently. Despite the treatment in mid-February 2017, the child again had a severe clinical relapse with significant inflammatory activity. She had a fever, maculopapular rashes, systemic inflammatory response. In March 2018, Adalimumab was again changed to Tocilizumab as joint inflammation did not subside. After three injections of the Tocilizumab, the child's body temperature returned to normal, skin rashes disappeared, laboratory markers of inflammation began to normalize, but the articular syndrome intensified. The child became practically immobilized. By the end of May 2018, the child's condition was very severe. The child had around-the-clock stiffness and a sharp restriction of movement in all small and large joints. She was immobilized and could not even change her body position in bed without assistance.

In June 2018, the parents took the child to Istanbul (Turkey) for treatment. Treatment included three pulses of methylprednisolone, 30 mg/kg each followed by oral methylprednisolone according to the scheme: the first three days, the child received 60 mg per day (3 mg/kg); the next three days - 32 mg per day; then 16 mg per day for one week; then 8 mg per day for one week; then 4 mg per day for one week with gradual weaning off steroids. Corticosteroids were also injected intra-articular in the knees, and treatment while continuing Tocilizumab. The child's condition improved on the treatment.

Due to refractoriness and intense disease activity, a genetic examination was done. Genetic examination revealed homozygous R202Q mutation and heterozygous V726A mutation in her *MEFV* (Mediterranean Fever) gene. A detailed study of the genealogical history established that all maternal relatives were Jews, but none of them had a recurrent fever and/or FMF.

The child was treated with Colchicine 15 mg 2 times a day and showed a favorable response. She is still receiving Tocilizumab, MTX, calcium, vitamin D, and folic acid.

Since the treatment adjustment 2021, the child's condition has stabilized. On physical examination, she has no joint pain or swelling, but persistent deformities of her joints. She has movement limitations in the shoulders, hip joints, and cervical spine. Her height is 152 cm, the bodyweight is 32.0 kg, BMI is 13.9 kg/m<sup>2</sup>, CRP is negative, ESR is 4 mm/hr, WBC is 7.1×10<sup>3</sup>/μL, platelets are 291×10<sup>3</sup>/μL, and Hb is 14.0 g/dL.

**DISCUSSION** This patient was initially diagnosed with systemic-onset JIA. The diagnosis of systemic-onset JIA was based on the clinical presentation, which included the patient's symptoms, age, and chronicity of arthritis in the joints. Ultrasound examination confirmed synovitis in >5 joints supporting a diagnosis of polyarthritis. Laboratory findings, including an elevated CRP, ESR, WBC and platelets, anemia, and the absence of ANA and rheumatoid factor, all further supported the diagnosis of RF-negative polyarthritis. Based on the patient's diagnosis and severity of her condition, she was treated with methylprednisolone, disease-modifying anti-rheumatic drugs (DMARDs), and MTX was added. The patient's arthritis was resistant to non-biological DMARD therapy. For those patients resistant to conventional DMARD therapy, biological agents are new therapeutic options. Biological therapy was started with Tocilizumab, which was now licensed in the EU for use alone or in combination with DMARDs to treat children over two years of age with the systemic or polyarticular form of JIA [17]. A genetic examination was performed in a Turkish clinic after seven years from the onset of the disease due to refractoriness and intense disease activity. Genetic examination revealed homozygous R202Q mutation and heterozygous V726A mutation in her *MEFV* (Mediterranean Fever) gene. *MEFV* gene mutations are observed in systemic-onset JIA. In addition to increasing the risk of JIA development, they seem to worsen the disease prognosis. This may have resulted from unsuccessful suppression of inflammation by pyrin, a protein known to be encoded by the *MEFV* gene. Due to *MEFV* mutations with the defect in pyrin functions, uncontrolled production of active IL-1β was also suggested. Thus, in systemic-onset JIA patients with *MEFV* mutations, these mechanisms contribute to inflammation, further worsening the clinical progression [11, 14].

The *MEFV* gene is also responsible for Familial Mediterranean Fever, which is an autosomal recessive disorder. The diagnosis of FMF is based on the clinical criteria of Tel Hashomer. These criteria contain three major (recurrent febrile episodes accompanied by serositis; amyloidosis of AA type; favorable response to colchicine) and three minor criteria (FMF in first-degree relatives; erysipelas-like erythema; recurrent febrile episodes); for diagnosis of FMF, it needs two major or one major plus two minor criteria [18]. There are no specific laboratory tests to diagnose FMF. During the attacks, serum CRP, fibrinogen, amyloid A, ESR, and leukocyte count increase. FMF is diagnosed according to clinical

findings, history, family history, and response to colchicine treatment. In addition, especially in suspected cases, demonstration of *MEFV* gene mutation is required. However, the diagnosis of FMF is sometimes difficult in patients with atypical symptoms and features [19].

In FMF, arthritis typically involves the lower extremities and tends to be monoarticular. Tenderness, swelling, and redness over the joint may be seen. Attacks usually subside in a few days; however, protracted arthritis, involvement of the upper extremities, and seronegative spondyloarthropathy have been reported. Arthritis is asymmetrical and non-destructive, except for the sacroiliac and hip joints [14, 20]. In addition to her history, the present patient had bilateral, symmetric arthritis of the large and small joints indicating the presence of JIA.

Ultimately, this patient met one of the major and one of the minor criteria of Tel-Hashomer: favorable response to colchicine and recurrent febrile episodes. There was no family history of FMF. The rheumatologist reports no signs of pleuritis, pericarditis, or peritonitis. It is known that FMF cases are most reported in races living in the Mediterranean region and are not typical for the Ukrainian population.

In conclusion, this case confirms the difficulties in diagnosing and treating sJIA associated with FMF. Currently, there are no established criteria for the definition or differential diagnosis of arthritis associated with FMF. In JIA patients with symptoms like abdominal pain, chest pain, fever, or resistant arthritis, FMF should be considered in the differential diagnosis. A modifier role of pyrin could be responsible for this severe involvement and resistance to DMARD therapy.

**CONCLUSION** Systemic onset JIA and FMF have some common pathogenic features. The presence of a *MEFV* gene mutation may potentiate the inflammatory response and thus act as a predisposing genetic factor in systemic-onset JIA or may cause the disease to have a more aggressive course.

Awareness of these co-morbidities is important among rheumatologists for a timely and precise management plan. The severe prognosis of JIA associated with FMF should motivate clinicians to initiate aggressive therapy early on, combining methotrexate with colchicine early on in those with the twin diseases and rapidly adding biological therapy if the patient does not achieve a rapid remission. Tocilizumab is a choice for patients with more severe disease or fails to respond to IL-1 blocking agents.

However, an individualized approach for each patient is recommended.

#### Disclosure:

The author declares no conflicts of interest.

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