Diagnosis and Treatment of Systemic Juvenile Idiopathic Arthritis

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Systemic juvenile idiopathic arthritis (SJIA) is an important disease for primary care physicians to keep in mind while managing a child with fever without an obvious source. This inflammatory condition manifests with high spiking fevers (classically quotidian or daily) and arthritis, and may be associated with evanescent rash, lymphadenopathy, hepatosplenomegaly, and serositis. Arthritis can occur later in the disease course, making initial diagnosis challenging. Although SJIA remains a clinical diagnosis of exclusion, without definitive diagnostic tests available, new insights into the biology of SJIA have changed the management of this condition. These scientific advances, plus the availability of new biologic therapies against targeted inflammatory cytokines (such as interleukin [IL]-1 and IL-6) have radically altered therapeutic approaches and dramatically improved disease outcomes. We review important advances in SJIA with key points for the diagnosis and management of SJIA (**Table I**).

Clinical Features

SJIA can be challenging diagnostically even for the senior clinician. SJIA comprises ≤15% of juvenile idiopathic arthritis (JIA) and can affect males or females with equal frequency.[1] The "classic" presentation of SJIA is daily or quotidian fever and arthritis. Characteristically, fever rises to >39°C and returns to normal for most of a 24-hour period. There may be an associated "salmon pink," evanescent (not fixed), macular rash (occasionally the rash may be raised and look like hives) that often is more prominent with fever spikes. The rash of SJIA usually is present on the trunk, back, or extremities and may show evidence of Koebnerization (appearance of rash along lines of trauma or scratching; **Figure**). Children also can manifest serositis, such as with pleural or pericardial effusion (chest pain and/or shortness of breath) or peritonitis (abdominal pain). These children can have evidence of hepatosplenomegaly and generalized lymphadenopathy. Some children have pulmonary involvement, including the later development of pulmonary hypertension or interstitial lung disease.[2] Children with typical presentation of SJIA often have laboratory evidence of significant systemic inflammation, including leukocytosis (often quite marked), significant thrombocytosis, anemia (of chronic inflammation), elevated inflammatory markers including erythrocyte sedimentation rate and C-reactive protein (CRP), and sometimes elevated D-dimer or ferritin level.[3] Almost all children with SJIA have negative tests for antinuclear antibody or negative rheumatoid factor, or both. To classify a patient as having SJIA by current International League of Associations for Rheumatology (ILAR) criteria, children should have ≥2 weeks of daily fever that is documented to be quotidian for ≥3 days, plus arthritis, plus any 1 of the following: nonfixed/evanescent rash, serositis, organomegaly, or lymphadenopathy (**Table II**).[4] Arthritis (swelling with pain or limitation of range of motion) can involve any joint, but often is not present at disease onset and results in delayed diagnosis. Only about 30% of children diagnosed with SJIA met the ILAR criteria for diagnosis at initial presentation of disease.[1] When the Yamaguchi criteria for adult-onset Still disease (considered the adult counterpart of SJIA; **Table II**) and the ILAR criteria were applied to a cohort of 31 children with SJIA, 13 did not meet the ILAR criteria for SJIA diagnosis (mainly owing to the absence of arthritis). However, 12 of these 13 children met the Yamaguchi criteria for diagnosis.[5,6]

Approximately one-third of children with SJIA present with occult macrophage activation syndrome (MAS), a potentially life-threatening condition necessitating rapid recognition and treatment. MAS (also known as secondary hemophagocytic lymphohistiocytosis) is a process of rapid expansion and activation of macrophages and T lymphocytes leading to "cytokine storm." Children with MAS can have "nonclassic features," including continuous rather than quotidian fever or fixed rash or both. Additionally, depending on the severity of MAS, myocarditis, renal dysfunction, hepatic dysfunction, bleeding owing to coagulopathy, and respiratory or central nervous system involvement can be present.[7] MAS can be associated with cardiopulmonary arrest and significant mortality. Children with MAS usually have laboratory evidence of cytopenias (thrombocytopenia, leukopenia), elevated serum hepatic enzymes, coagulopathy (elevated D-dimer, prolonged prothrombin time, and decreasing fibrinogen), decreasing erythrocyte sedimentation rate (owing to consumption of fibrinogen), elevated triglycerides, elevated lactate dehydrogenase, and hyperferritinemia. Bone marrow evaluation shows evidence of hemophagocytosis in

CRP	C-reactive protein
FDA	US Food and Drug Administration
IL	Interleukin
ILAR	International League of Associations for Rheumatology
JIA	Juvenile idiopathic arthritis
MAS	Macrophage activation syndrome
SJIA	Systemic juvenile idiopathic arthritis
TNF	Tumor necrosis factor

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Table I. Key points in diagnosis and management of SJIA

- Classic SJIA has a quotidian fever pattern and typical erythematous or pink, macular, evanescent rash.
- There are no laboratory tests for diagnosis of SJIA. SJIA remains a clinical diagnosis of exclusion and it is important to rule out infection or malignancy as the cause of fevers before treatment.
- Initial assessment of SJIA should include evaluation for the serious life-threatening complication of MAS.
- MAS can present with continuous (rather than quotidian) fevers, fixed (rather than evanescent) rash, and laboratory evidence of low platelets, white blood cell counts, fibrinogen, erythrocyte sedimentation rate and elevated liver function tests, lactate dehydrogenase, D-dimers, prothrombin time, triglycerides, and ferritin.
- Anti-IL1 and anti-IL6 therapies have dramatic benefit in SJIA and there may be an early "window of opportunity" during which rapid and effective therapy may improve long-term outcomes.

≤60% of patients.[7] Early recognition of the potentially life-threatening complication of MAS is facilitated by monitoring white blood cells, platelet count, erythrocyte sedimentation rate, ferritin, fibrinogen, and D-dimer measurements. International expert panels recently have developed consensus diagnostic and validated classification criteria for MAS specifically in patients with SJIA.[8] However, it is important to suspect and treat patients when they seem to be developing MAS, rather than waiting for complete criteria for diagnosis.

Diagnosis

The diagnosis of SJIA remains a clinical one of exclusion. There are no definitive laboratory tests to distinguish SJIA from other febrile illnesses. Treating physicians must rule out other causes of fever, including infections, malignancy, and other inflammatory/rheumatologic conditions such as Kawasaki disease, systemic lupus erythematosus, and periodic fever (autoinflammatory) syndromes (such as cryopyrin-associated periodic fever syndrome or familial Mediterranean fever). This is especially important before initiating corticosteroid therapy, because this may mask malignancy temporarily, alter its response to treatment, and change the eventual outcome. Children suspected to have SJIA must always undergo a thorough and complete evaluation for infection and malignancy, including cultures of blood and urine, imaging studies (echocardiogram if Kawasaki disease is suspected, computed tomography of the chest and abdomen to exclude malignancy), and sometimes bone marrow examination (especially if cytopenias are present) or lymph node biopsy to exclude leukemia or lymphoma, respectively. Many studies have been performed attempting to identify potential diagnostic biomarkers of SJIA. A recent review summarized the utility of various serum (including ferritin, IL-18, S100 protein levels), cellular (monocyte subsets), and gene expression profiling studies in SJIA.[9] Although not available commercially, the S100 proteins (S100A12 and S1000A8/9 [calprotectin]) seem to hold promise to help distinguish SJIA from other febrile illnesses.[10-12] One study used an enzyme immunoassay panel to analyze seven plasma proteins (consisting of alpha-2-macroglobulin, apolipoprotein A-1, CRP, haptoglobin, calprotectin, serum amyloid A, and serum amyloid P) to distinguish SJIA from other causes of fever.[13] If MAS is suspected, increased levels of soluble CD163 or soluble IL-2 receptor α, and decreased natural killer cell dysfunction, can be demonstrated in addition to the other laboratory abnormalities as mentioned.[14-16] In patients with MAS, physicians may consider genetic testing for polymorphisms in primary hemophagocytic lymphohistiocytosis syndrome genes.

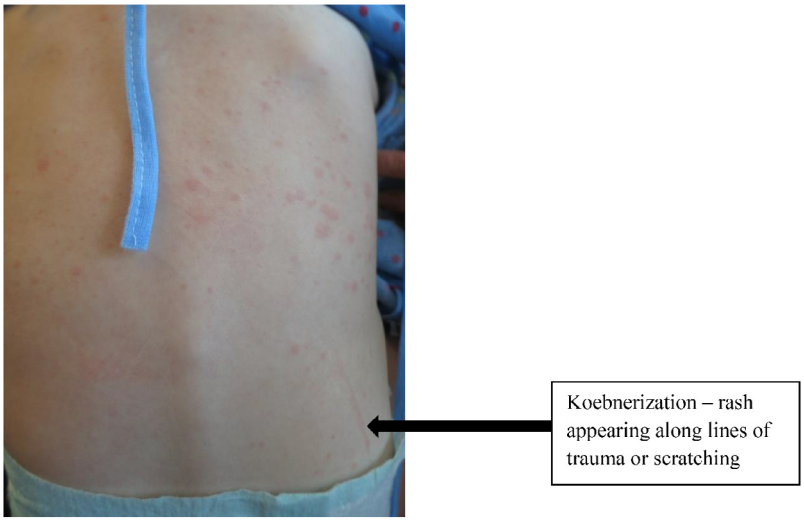

Figure. SJIA rash—nonfixed or evanescent pink or erythematous macules. (Image courtesy of Dr Clayton Sontheimer.)