Juvenile Idiopathic Arthritis: A Chronic Pediatric Musculoskeletal Condition with Significant Orofacial Manifestations

Torin Barr, BSc, DDS; Nicole M. Carmichael, PhD; George K.B. Sándor, MD, DDS, PhD, FRCD(C), FRCSC, FACS

ABSTRACT

Juvenile idiopathic arthritis (JIA), a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, begins before 16 years of age. The hallmark feature of JIA is chronic inflammation of the joints, but the term encompasses several disease categories. The cause of JIA is still poorly understood and none of the available drugs for JIA can cure the disease. However, the prognosis has greatly improved as a result of progress in disease classification and management. The dental practitioner should be familiar with the symptoms and oral manifestations of JIA to help manage this disease.

Like other forms of arthritis, JIA is characterized by inflammation of the synovium of one or more joints. However, the term JIA has replaced previous terms such as juvenile chronic arthritis or juvenile rheumatoid arthritis to more accurately identify homogenous groups of children with distinct clinical features. The International League of Associations for Rheumatology (ILAR), which has provided the most recent classification, identifies 7 subtypes of JIA with specific exclusion and inclusion criteria (Tables 1 and 2). Females are much more frequently affected with almost all types of JIA than males. The worldwide prevalence of JIA varies between 16 and 150 per 100,000; the frequency of different subtypes of JIA vary with location and ethnicity.
### Table 1 ILAR classification, inclusion and exclusion criteria, frequency and sex distribution of JIA

<table>
<thead>
<tr>
<th>Classification</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Frequency (%)</th>
<th>Sex ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis</td>
<td>Onset age: throughout childhood Number of joints affected: variable Systemic features: quotidian fever + ≥ 1 of the following: erythematous rash, myalgias, lymphadenopathy, hepatosplenomegaly or serositis.</td>
<td>N/A</td>
<td>4–17</td>
<td>F = M</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>Onset age: early childhood, peak 2–4 years Number of joints affected: persistent: ≤ 4; extended: ≥ 4 joints after the first 6 months Psoriasis/family history HLA B27 RF-positive Males &gt; 6 years</td>
<td>27–56</td>
<td>Three times greater in F than M</td>
<td></td>
</tr>
<tr>
<td>RF-positive polyarthritis</td>
<td>Onset age: late childhood, adolescence Number of joints affected: ≥ 5 joints Serological test: IgM RF-positive</td>
<td>IgM RF-negative</td>
<td>2–7</td>
<td>Twice as great in F than M</td>
</tr>
<tr>
<td>RF-negative polyarthritis</td>
<td>Onset age: biphasic distribution, early peak 2–4 years, later peak 6–12 years Number of joints affected: ≥ 5 joints Serological test: IgM RF-negative</td>
<td>IgM RF-positive</td>
<td>11–28</td>
<td>Twice as great in F than M</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>Onset age: late childhood or adolescence Number of joints affected: variable, usually ≤ 4 Other diagnoses: enthesitis</td>
<td>N/A</td>
<td>3–11</td>
<td>Twice as great in F than M</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Onset age: biphasic distribution, early peak at 2–4 years, late peak at 9–11 years Number of joints affected: variable, usually ≤ 4 Other diagnoses: psoriatic rash, family history of psoriasis, dactylitis or nail pitting</td>
<td>N/A</td>
<td>2–11</td>
<td>Greater in F than M</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>Onset age: N/A Patients who do not satisfy inclusion criteria for any other category</td>
<td>N/A</td>
<td>11–21</td>
<td>No known sex predilection</td>
</tr>
</tbody>
</table>

ILAR = International League of Associations for Rheumatology; JIA = juvenile idiopathic arthritis; N/A = not applicable; F = female; M = male; HLA = human histocompatibility leukocyte antigen; RF = rheumatoid factor.

*A child is diagnosed with a specific subtype of juvenile idiopathic arthritis if he or she falls into one of the categories listed here. Adapted from Ravelli and Martini.*

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**Figure 1a:** Lateral cephalogram showing that severe juvenile idiopathic arthritis (JIA) can result in striking facial deformities with “bird-like” facies due to severe retrognathia and loss of posterior vertical dimension from condylar resorption.

**Figure 1b:** Panoramic radiograph showing severe condylar resorption and accentuated bilateral antegonial notching.
Pathogenesis

Inflammation of the synovium is a key pathological feature of JIA. However, the exact trigger and factors that allow the inflammation to become chronic are not clearly understood. The prevailing view is that both inherited and environmental factors are important and that an autoimmune reaction precipitates a cascade of inflammatory changes.4 Once an immune response is initiated and inflammation in the joint is triggered, B lymphocytes produce immunoglobulins; in some subsets of JIA, rheumatoid factors of the IgG and IgM classes are deposited in the sublining layer of the synovium. This response subsequently activates the serum complement cascade and recruits the phagocytic arm of the immune response, which further exacerbates the inflammation of the synovium, leading to edema, vasodilation and infiltration of activated T cells.5,6

Early and intermediate molecular mediators of inflammation have been identified in the synovium of some patients with JIA and include tumour necrosis factor alpha; interleukins IL-1, IL-6, IL-8 and IL-15; transforming growth-factor beta; fibroblast growth factor; and platelet-derived growth factor7-10 — all of which contribute to the breakdown of collagen and the proteoglycan matrix of articular cartilage. Once the inflammation is established, the synovium thickens, the cartilage and the underlying bone begins to disintegrate, and evidence of joint destruction occurs.8-11

Genetic factors and specific gene loci are important in the pathogenesis of JIA.12 Several genes, including at least 1 gene in the human histocompatibility leukocyte antigen (HLA) region, affects susceptibility to JIA. However, different subsets of JIA are associated with different HLA and non-HLA regions, which likely accounts for the heterogeneity of the disease. In predisposed children, environmental triggers, such as exposure to sunlight or cigarette smoke, drugs or infection may precipitate the development of JIA.4

Clinical Presentation

The diagnosis of JIA, according to the ILAR classification, requires specific clinical features, including distinct methods of presentation such as systemic, polyarticular involving many joints, oligoarticular involving 4 or fewer joints, the age of onset and the results of serological testing.4 Table 1 outlines the ILAR’s diagnostic criteria for each subtype of JIA.

Differential Diagnosis

Several diseases mimic the initial course of JIA, thus making its differentiation from other conditions difficult. Differential diagnosis of systemic JIA includes infection, malignancy, rheumatic fever, connective-tissue diseases, inflammatory bowel disease, Castleman’s disease and autoinflammatory syndromes4 (Table 3).
Treatment

Management of JIA is based on a combination of pharmacological interventions (Table 4), physical and occupational therapy, and psychosocial support. The aim of the treatment is to control the disease, and prevent further progression and any long-term effects related to the disease or treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of the treatment of this disease for decades. Most children with JIA are started on NSAIDs; however, only a few NSAIDs are approved for use with children. The most common include naproxen, ibuprofen and indomethacin. They are generally well tolerated and have few side effects.

Intra-articular steroid injections with triamcinolone hexacetonide are frequently needed at the onset and during the course of the disease. For monoarticular or oligoarticular arthritis, they may be used with or without NSAIDs. These steroids are effective rapidly and help prevent deformities.

Patients whose disease is not well controlled by these approaches or by physical therapy are candidates for more aggressive interventions. Moderate- or high-dose systemic corticosteroid therapy is reserved for patients with systemic JIA whose disease is not controlled by NSAIDs. Corticosteroids are used very selectively because of their potential toxic effects (Box 1), including growth arrest and retardation, and osteopenia. Bisphosphonates may be given to these children to try to combat the osteopenic effects of chronic treatment with systemic corticosteroids.

Methotrexate has become the second line treatment of choice for persistent active arthritis because of its effectiveness and acceptable toxic effects. Improvements are usually seen after 6 to 12 weeks, and supplementation with folic acid can help prevent the occurrence of liver-enzyme abnormalities that can occur as a result of methotrexate treatment. The use of methotrexate in pediatric rheumatology practice is very different from the treatment regimens of other specialties such as oncology. Doses are smaller in pediatric rheumatology, but regimens are longer-term. As a result, oral ulceration, mucositis and bone-marrow suppression are rare, and the risk of opportunistic infection is lower for patients with JIA than for oncology patients.

The introduction of biological medications has also provided an important new therapeutic option for the treatment of patients with JIA who are resistant to antirheumatic agents. Etanercept (0.4 mg/kg, given subcutaneously twice weekly) is very effective for patients who have polyarticular disease and are resistant or intolerant to methotrexate. Etanercept is generally well tolerated, but patients should be monitored for potential side effects related to its long-term use.

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Table 3 Common differential diagnoses of systemic JIA

<table>
<thead>
<tr>
<th>Infection</th>
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<tr>
<td>Septicemia</td>
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<td>Bacterial endocarditis</td>
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<tr>
<td>Brucellosis</td>
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<tr>
<td>Typhoid fever</td>
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<tr>
<td>Leishmaniasis</td>
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<tr>
<td>Viral infections</td>
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<table>
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<tr>
<th>Malignancy</th>
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<tbody>
<tr>
<td>Leukemia</td>
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<td>Lymphoma</td>
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<td>Neuroblastoma</td>
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<table>
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<tr>
<th>Rheumatic fever</th>
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<tr>
<td>Connective tissue disease</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Kawasaki syndrome</td>
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<td>Polyarthritis</td>
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<tr>
<th>Inflammatory bowel disease</th>
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<tr>
<td>Castleman’s disease</td>
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| Autoinflammatory syndromes                    |

| JIA = juvenile idiopathic arthritis. |

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Table 4 Pharmacological treatments used in patients with JIA

<table>
<thead>
<tr>
<th>Nonsteroidal anti-inflammatory drugs</th>
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<tbody>
<tr>
<td>Naproxen</td>
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<tr>
<td>Ibuprofen</td>
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<td>Indomethacin</td>
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<table>
<thead>
<tr>
<th>Intra-articular steroids</th>
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<tbody>
<tr>
<td>Triamcinolone hexacetonide</td>
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<table>
<thead>
<tr>
<th>Systemic steroids</th>
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</thead>
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<tr>
<td>Prednisone</td>
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<table>
<thead>
<tr>
<th>Methotrexate</th>
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<tbody>
<tr>
<td>Etanercept</td>
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</table>

| Anti-IL-1 or anti-IL-6 drugs                  |

| JIA = juvenile idiopathic arthritis. |

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Box 1 Side effects of long-term corticosteroid intake

- Compromised immunity
- Atherosclerosis
- Hypercholesterolemia
- Hyperglycemia
- Cushingoid appearance
- Acne
- Cataracts
- Avascular necrosis of the hip
- Severe osteoporosis
- Pharmacologically induced adrenal insufficiency
Chronic arthritis in children has a negative effect on bone development, develops chronic arthritis as the major long-term complaint of patients, systemic symptoms resolve and the patient develops complete remission, although patients may have several years of complex potent immunosuppressive treatments. For many children, the expectation of methotrexate and other immunosuppressives, result in improved outcomes. For many children, the expectation is complete remission, although patients may have several years of complex potent immunosuppressive treatments. Systemic JIA has the most variable course. In 50% of patients, systemic symptoms resolve and the patient develops chronic arthritis as the major long-term complaint. Chronic arthritis in children has a negative effect on bone and joint development. Local growth disturbances take place at the sites of inflammation and result in either overgrowth, possibly related to inflammation-induced increased vascularization and growth-factor release; or undergrowth, secondary to growth-centre damage or premature fusion of epiphyseal plates of the juxta-articular bone extremities. Anomalies in the growth and morphogenesis of skeletal segments also result from irregular bone growth and development of the hip are examples of possible results of these processes. In severe cases of systemic JIA, the disease and its treatment with steroids can cause severe growth retardation and osteoporosis. As a consequence, these patients may also receive bisphosphonate therapy to prevent steroid-induced osteoporosis.

**Oral Manifestations of JIA**

Patients with JIA may have a variety of dentofacial complications related to the disease or disease treatment (Box 2). The possible dentofacial manifestations of JIA have been grouped into oral and dentoskeletal findings.

Oral manifestations associated with JIA include increased dental caries, poor oral hygiene and malocclusion. Patients with JIA have a higher caries index, and more decayed, filled and missing teeth than age-matched groups, as well as increased frequency of decayed teeth in all major age groups. Oral hygiene is poor across all age groups. Poor oral hygiene may be a result of upper-limb involvement, which may affect the patient’s ability to brush teeth with fine-motor movements required for efficient tooth brushing and flossing.

A second factor affecting the increased incidence of caries may be the medications patients use to control inflammation. The primary medical treatments involve the use of NSAIDs and disease-modifying antirheumatic drugs (DMARDs). Use of NSAIDs, which is advocated as a first-line therapy, results in improvement in 50% of patients within 2 weeks and in the remainder within 8 weeks. Given the young age of many of these patients, pill or tablet formulations are often not well tolerated. As a result, practitioners use elixir forms, a large percentage (59%–65%) of which are sugar-based. The repeated exposure to a high dose of sugars, combined with a limited ability to attain proper oral hygiene, contributes to the overall increased incidence of caries seen in this patient group. Some sugar-free forms of medication are available and should be recommended to the patients’ physicians when possible.

DMARDs, the second line of treatment, are safe and effective alternatives to NSAIDs. The most popular agent is methotrexate. It seems to cause fewer side effects in children than in adults and is effective for 60% to 70% of patients. The once weekly dosing regimen makes it especially appealing for pediatric patients because non-

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**Box 2 Orofacial findings for JIA**

- Temporomandibular joint: limited opening with progressive open bite.
- Effect on mandibular growth: retrognathia.
- Effect on upper limb function with swollen joints in the hands: difficulty with fine-motor movements required for tooth brushing and flossing.
- Medications:
  - Oral medications associated with increased caries risk because of sugar content of elixir formulations.
  - Methotrexate possibly resulting in stomatitis or oral ulceration.
  - Cyclosporine, although infrequently used, possibly causing gingival hyperplasia, blood dyscrasia, renal impairment and hypertension.
- Salivary abnormalities: lower levels of Ca++, PO4, K+, lysozyme and IgA than those of healthy controls.

**JIA = juvenile idiopathic arthritis.**

patients with systemic arthritis who are unresponsive to NSAIDs, methotrexate or etanercept, or a combination of anti-interleukin-1,6 therapies have been very successful in recent clinical trials.

These children, who may be taking combinations of potent immunosuppressives, including methotrexate, biologics and steroids, are at constant risk of potential infection and bacteremia. Systemic features of sepsis may be altered by the immunosuppression, especially by the biologics. A child with well-controlled JIA whose condition flares up for no apparent reason may well have occult dental sepsis, including abscess.

Physiotherapy and occupational therapy are important components of the therapeutic approach to any patient with JIA. Arthroscopic synovectomy or soft-tissue release can be helpful in select cases. Total arthroplasty of the hip and knee, a successful option if the patient is severely functionally impaired, is usually delayed until growth has stopped.

**Prognosis and Outcome**

Many of the reports of poor outcome and disability reflect the treatment of decades ago. Current changes in the management of JIA, such as early and aggressive use of methotrexate and other immunosuppressives, result in improved outcomes. For many children, the expectation is complete remission, although patients may have several years of complex potent immunosuppressive treatments.

Systemic JIA has the most variable course. In 50% of patients, systemic symptoms resolve and the patient develops chronic arthritis as the major long-term complaint. Chronic arthritis in children has a negative effect on bone development. Local growth disturbances take place at the sites of inflammation and result in either overgrowth, possibly related to inflammation-induced increased vascularization and growth-factor release; or undergrowth, secondary to growth-centre damage or premature fusion of epiphyseal plates of the juxta-articular bone extremities. Anomalies in the growth and morphogenesis of skeletal segments also result from irregular bone growth and development of the hip are examples of possible results of these processes. In severe cases of systemic JIA, the disease and its treatment with steroids can cause severe growth retardation and osteoporosis. As a consequence, these patients may also receive bisphosphonate therapy to prevent steroid-induced osteoporosis.
compliance is less of an issue. However, methotrexate is not without side effects: it may result in painful stomatitis and oral ulcerations in some patients, which may be minimized with folic-acid supplementation. Cyclosporine, infrequently used for treatment of JIA, is limited by its significant side effects, including hirsutism and gingival hyperplasia.

Patients with JIA who have decreased levels of Ca++, PO₄, K⁺, lysozyme and IgA have more salivary abnormalities than healthy controls. Patients with JIA often have malocclusion because of the effects of the disease on the temporomandibular joint (TMJ) and facial growth. These patients often have Class II molar and canine relationships, and many also have an anterior open bite because of the progressive loss of the posterior vertical dimension from progressive condylar resorption (Figs. 2a and 2b).

Dentofacial Consequences of JIA

The dentofacial consequences of JIA are based on changes within the structures of the TMJ and their resultant effects on mandibular growth (Figs. 1a to 2b). Reports of TMJ involvement in JIA range from 17% to 87%. About 45% of cases may be diagnosed from radiographic changes on an orthopantogram. The incidence of TMJ joint involvement is variable, depending on the age of the study, the source of the patients and the methods used to define the involvement. TMJ involvement is not uncommon, and though it is often identified with ultrasound and MRI, it may be subclinical. Micrognathia and retrognathia, which are less common because of their current management with methotrexate and biologicals, usually manifest in children with severe refractory disease or those who received pediatric rheumatology care late in the course of their disease. Such radiographic changes, if present, include shortening of the mandibular body and ramus, flattening of the condyles and increased antegonial notching (Figs. 3a to 3c).

As with their other joints, patients with JIA and involvement of the TMJ may complain of morning stiffness of the joint, along with trismus, reduced interincisal opening, reduced ability to translate and possible clicking or crepitation. Pathologic changes within the condylar head are thought to adversely affect the growth potential of the region, which results in the characteristic changes associated with JIA.

Patients with JIA typically present with posterior or downwards mandibular rotation, a steep mandibular plane and mandibular retrognathia. Associated
with the mandibular changes are an increased vertical growth of the anterior face and possible anterior open bite. As a result, in the most severe cases, some authors described these patients as having a “bird-face” deformity (Figs. 1a and 1b). The frequency and severity of facial changes are correlated with the JIA type; polyarticular forms have the greatest impact on facial growth and the final form of the face. These patients often require even more complex surgical management (Figs. 4a to 4e).

Sedation and general anesthesia must be administered to these patients with caution because some may have neck involvement and cervical-spine instability. The cervical spine must therefore be assessed in the workup of these patients.

**Dental Management of JIA Patients**

Dental management of patients with JIA is based on prevention of dental disease. Regular dental checkups that include extensive instruction about oral hygiene play an important role. For patients with upper-limb involvement, electric toothbrushes are recommended to help promote better debridement. Fluoride treatments, dietary changes and sealants should be used as needed. Sugar-free formulations of patient medications should be used whenever possible. Opening exercises to ensure adequate range of motion of the TMJ have also been suggested. Orthodontic appliances, applied during the prepubertal growth spurt may help minimize changes in occlusion and aid mandibular growth. The role of the dentist in optimizing the dental care of these unique patients and in increasing pediatricians’ and pediatric specialists’ awareness about their oral health cannot be overstressed.

Orthodontic treatment may help manage these patients’ malocclusions, up to a point. In those cases of JIA in which the facial deformity is severe, orthognathic surgery may be considered. However, jaw surgery is not advocated until the systemic aspects of the disease have been fully controlled. These patients have a high potential for skeletal relapse. Orthognathic surgery should be undertaken only once the TMJ and occlusal findings have stabilized. The interincisal opening can be measured serially at recall visits over time. The continued progressive worsening of an open bite in patients with JIA is a contraindication to orthognathic surgery, especially if the condyles are actively undergoing a lytic phase. The risk for these patients is similar to the risks that patients...
with idiopathic condylar resorption face when they have orthognathic surgery.

Conclusions

Patients with JIA face long-term, if not lifelong, consequences of their disease that may involve more than their musculoskeletal system. They may also have significant dental morbidity, which is preventable. These patients require close supervision to guard against dental caries. They frequently require orthodontic intervention and, in selected cases, may eventually benefit from orthognathic surgery.

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References

Juvenile Idiopathic Arthritis (JIA) is an autoimmune heterogeneous disease with a spectrum of joint involvement and associated systemic involvement. This disease is characterized by joint inflammation with symptoms persisting for more than six weeks and onset before 16 years of age [1]. The worldwide prevalence of JIA ranges from 16 to 150 per 100 000 [2], with an annual incidence from 3.2 to 24 per 100 000 [3–8].


Juvenile rheumatoid arthritis (JRA) is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases of childhood (see the image below). The etiology is unknown, and the genetic component is complex, making clear distinctions between the various subtypes difficult.


Juvenile idiopathic arthritis (JIA) is a group of conditions with distinct clinical phenotypes and likely differing underlying pathogenic mechanisms. The heterogeneity of JIA at pathologic and immunologic levels is informative in driving the understanding of these diseases. Infiltrating inflammatory cells interact with each other and resident synovial fibroblasts, promoting a chronic inflammatory process in the synovial membrane and secreted synovial fluid (Figure 106-1). In this chapter, we discuss the genetic factors that predispose to JIA and the abnormalities that underlie synovial and systemic inflammation.