Pediatric Systemic Lupus Erythematosus, Dermatomyositis, Scleroderma, and Vasculitis

RONALD M. LAXER • SUSANNE M. BENSELER

understanding of these diseases and enabled us to recognize novel inflammatory diseases and their mimics.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition and Classification

Pediatric SLE (pSLE) is a chronic multisystem autoimmune disease with remitting, relapsing course and onset of symptoms before age 18 years, accounting for approximately 20% of all SLE.1 This clinically heterogeneous disease is characterized by a distinct spectrum of autoantibodies including antinuclear antibody (ANA), double-stranded deoxyribonucleic acid (dsDNA), and antibodies against extractable nuclear antigens (ENAs). In genetically susceptible hosts B cell–mediated autoimmune processes lead to a variable combination and severity of clinical symptoms including antibody-mediated vasculitis, direct antibody binding to target cells, and thrombotic organ dysfunction.

The American College of Rheumatology (ACR) classification criteria for adults with SLE are commonly applied to children with pSLE.2 The classification of neuropsychiatric SLE (NPSLE) in children and adolescents remains a challenge.3,4 The 1990 ACR NPSLE nomenclature and case definitions appear to have limited applicability for children in certain domains.5-7

Epidemiology

Pediatric SLE affects children and adolescents around the world.8-10 On average, 60% of patients develop pSLE after age 10, 35% between 5 and 10 years, and only 5% before age 5. In studies from Asia, the mean ages at diagnosis were reported to be 8.6 to 13.5 years.8,9 The incidence and prevalence of pSLE varies between populations. Similar to adults, SLE more commonly affects non-Caucasian populations.8,9,11 Overall, incidence rates of pSLE have been reported to be 0.28 to 0.48 per 100,000 children with prevalence rates of 6.3 to 24 per 100,000 depending on the ethnic background of the population.9 The prevalence of pSLE is consistently higher in girls than boys: Canadian and Taiwan studies estimated a factor of 6.12,13 Female predominance increases with age. This observation strongly supports the suggested role of female hormones.14 Although pSLE is less common than adult SLE, childhood onset was recently
found to be a strong, independent predictor of overall lupus mortality.\(^\text{15}\)

Children with pSLE are likely to have relatives with SLE. The pattern of familial aggregation for siblings with SLE suggests a polygenic inheritance.\(^\text{16}\) In addition, pSLE patients often have asymptomatic relatives with evidence of autoantibodies.\(^\text{17}\)

### Causes

#### Genes

Enabled by large international collaborations, susceptibility genes have been identified suggesting a dysregulated immune phenotype in lupus patients partially overlapping with other autoimmune diseases.\(^\text{18}\) These include genetic variants in the cytokine interferon-\(\alpha\) pathway and their functional impact,\(^\text{19}\) the contribution of signal transduction STAT4 gene variations on lupus susceptibility,\(^\text{20}\) and the association of the interleukin-1 receptor-associated kinase-1 (IRAK1), an X chromosome gene, and disease susceptibility in pSLE.\(^\text{21}\)

Beyond the type of gene variant (mutation, polymorphisms), altered copy number variations reflecting “gene dose” and epigenetic modifications of key lupus genes are reported in pediatric lupus patients: Garcia-Ortiz demonstrated an association of the lupus gene Toll-like receptor 7 (TLR7) copy number variation with susceptibility to pSLE in Mexican populations.\(^\text{22}\) Drug-induced SLE and incomplete monozygotic twin concordance rates suggest an important role of epigenetic factors such as histone modification or altered DNA methylation in pSLE.\(^\text{23}\) Finally, mitochondrial DNA polymorphisms may also be important in the pathogenesis of SLE.\(^\text{24}\) Children with inherited complement deficiencies including C2, C4A/C4B, C1q, and C1s can present with pSLE.\(^\text{25}\) These single gene defects are more commonly seen in familial cases of lupus.

#### Environment

Beyond genes and epigenetics, other potential contributing factors have been intensely studied in pSLE including environmental factors such as parental smoking\(^\text{26}\) and organic dust exposure.\(^\text{27}\) As a link between genetic and environmental factors, endogenous and external viruses are currently being studied in pSLE.\(^\text{28}\) The presence of an interferon signature pattern had raised suspicion for a potential viral contribution and discovery of the genetic basis of chilblain lupus.\(^\text{29}\) This focused the researchers’ attention to DNA repair of endogenous virus as a potential pathogenetic factor in pSLE.

#### Pathology

Similar to adult SLE, the inflammatory processes leading to organ dysfunction are heterogeneous between and within organs (see Chapter 79). Immunoglobulin deposition in small vessels such as glomerulus or lung capillaries, complement activation, antibody-binding to single cells, and microthrombotic or macrothrombotic vessel disease are the hallmarks of lupus. Hematologic manifestations of lupus are often related to direct antibody-binding and complement activation.\(^\text{30}\) In contrast, the histology of pediatric lupus nephritis is more variable and includes the distinct subtypes of mesangial, focal, or diffuse proliferative and membranous nephritis, which can coexist.\(^\text{31}\) Renal biopsies are required to distinguish subtypes and define treatment regimens. In children, severity of the glomerulonephritis on renal biopsy was shown to be associated with treatment choice and response and long-term outcome.\(^\text{32-34}\) Confounding risk factors for severe lupus nephritis and adverse renal outcome include evidence of thrombotic microangiopathy, antiphospholipid antibodies, tubulointerstitial disease, hypertension, nephrotic syndrome, and access to health care.\(^\text{31,35}\)

### Clinical Features

The clinical presentation of pSLE was reported in large series from many countries, allowing a better understanding of the clinical diversity, impact of ethnicity, confounding factors including infections, and access to health care\(^\text{8,11,36-47}\) (Table 108-1).

Systemic features including fever and fatigue are found in more than 90% of children at diagnosis of pSLE. Arthritis is the most frequently reported organ manifestation in pSLE. Typically pSLE arthritis is a nonerosive, painful polyarthritis. Mucocutaneous involvement includes the typical “butterfly” or malar rash, an erythematous rash in the malar distribution sparing the nasolabial folds (Figure 108-1). Diffuse hair loss is commonly seen in children with active disease. In addition, children with lupus can present with a photosensitive rash, exacerbated in sun-exposed areas including upper arms, neckline, and face; Raynaud’s phenomenon of fingers and toes; a vasculitic skin rash, which is often raised and painful affecting the fingers and toes; and oral and/or nasal ulcers. Oral ulcers are typically located on the hard palate and are painless (Figure 108-2). Uncommon skin manifestations include discoid lupus lesions, which heal with scarring.\(^\text{48}\)

Nephritis is the most common major organ manifestation and occurs in more than 50% of children with pSLE, most commonly at diagnosis. Children with lupus nephritis present with peripheral edema, proteinuria, active urine sediment, and hypertension. Focal or diffuse proliferative

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**Figure 108-1** Malar rash of a 14-year-old patient with pediatric systemic lupus erythematosus. The disease’s typical “butterfly” or malar rash is an erythematous rash in the malar distribution, which includes the cheeks and crosses the nasal bridge but spares the nasolabial folds.
Table 108-1  Clinical Characteristics of Children at Diagnosis of Pediatric Systemic Lupus Erythematosus (pSLE): Comparison of Four Recent Cohorts

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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Number of pediatric SLE patients</td>
<td>213</td>
<td>70</td>
<td>258</td>
<td>230</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>11.6 (±2.6)</td>
<td>10.5 (4-15)</td>
<td>13.1 (±3.2)</td>
<td>15.3 (13.2-16.7)</td>
</tr>
<tr>
<td>Female-to-male ratio</td>
<td>4.2:1</td>
<td>6:1</td>
<td>4.7:1</td>
<td>9:01</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>3.6 yr</td>
<td>NR</td>
<td>3.5 yr</td>
<td>1.7 yr</td>
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Generalized symptoms

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<th></th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>NR</td>
<td>NR</td>
<td>50%</td>
<td>NR</td>
</tr>
<tr>
<td>Fever</td>
<td>NR</td>
<td>92%</td>
<td>39%</td>
<td>NR</td>
</tr>
<tr>
<td>Weight loss</td>
<td>NR</td>
<td>30%</td>
<td>29%</td>
<td>63%</td>
</tr>
<tr>
<td>Lymphadenopathy/hepatosplenomegaly</td>
<td>NR</td>
<td>42%/47%</td>
<td>19%</td>
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</table>

Organ manifestations

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</thead>
<tbody>
<tr>
<td>Hematologic disease</td>
<td>NR</td>
<td>NR</td>
<td>55%</td>
<td>NR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>NR</td>
<td>24%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>NR</td>
<td>NR</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Coombs-positive hemolytic anemia</td>
<td>NR</td>
<td>58%</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>Mucocutaneous disease</td>
<td>NR</td>
<td>57%</td>
<td>61%</td>
<td>70%</td>
</tr>
<tr>
<td>Malar rash</td>
<td>NR</td>
<td>51%</td>
<td>17%</td>
<td>53%</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>NR</td>
<td>NR</td>
<td>21%</td>
<td>49%</td>
</tr>
<tr>
<td>Nasal ulcers</td>
<td>NR</td>
<td>NR</td>
<td>8%</td>
<td>NR</td>
</tr>
<tr>
<td>Arthritis</td>
<td>NR</td>
<td>66%</td>
<td>61%</td>
<td>83%</td>
</tr>
<tr>
<td>Nephritis</td>
<td>81% total</td>
<td>77% total</td>
<td>37% total</td>
<td>49% total</td>
</tr>
<tr>
<td>Mesangial—WHO Class II</td>
<td>47%</td>
<td>NR</td>
<td>15%</td>
<td>NR</td>
</tr>
<tr>
<td>Focal proliferative—WHO Class III</td>
<td>2%</td>
<td>NR</td>
<td>28%</td>
<td>NR</td>
</tr>
<tr>
<td>Diffuse proliferative—WHO Class IV</td>
<td>37%</td>
<td>NR</td>
<td>47%</td>
<td>NR</td>
</tr>
<tr>
<td>Membranous—WHO Class V</td>
<td>8%</td>
<td>NR</td>
<td>16%</td>
<td>NR</td>
</tr>
<tr>
<td>Neuropsychiatric disease</td>
<td>NR</td>
<td>21%</td>
<td>16%</td>
<td>NR</td>
</tr>
<tr>
<td>Serositis</td>
<td>NR</td>
<td>3%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>NR</td>
<td>3%</td>
<td>12%</td>
<td>17%</td>
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<tr>
<td>Pleuritis</td>
<td>NR</td>
<td>NR</td>
<td>1%</td>
<td>NR</td>
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<tr>
<td>Cardiac disease</td>
<td>NR</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>NR</td>
<td>NR</td>
<td>0.4%</td>
<td>NR</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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NR, not reported; WHO, World Health Organization.

glomerulonephritis accounts for more than 50% of all pediatric lupus nephritis in most series. Acute renal failure can occur in a third of children presenting with proliferative lupus nephritis. Mesangial and membranous nephritis are less common and can occur in conjunction with proliferative lupus nephritis. Posterior reversible encephalopathy (PRES) is an increasingly recognized central nervous system (CNS) complication of lupus nephritis and hypertension. Neuropsychiatric disease affects about a quarter of children with pSLE. Headaches in conjunction with psychosis or cerebrovascular disease presenting as seizures or severe cognitive dysfunction are the most common clinical phenotypes. Isolated lupus headache is uncommon. Psychosis in pSLE is characterized by optic and acoustic hallucinations and visual distortions. Many patients have overlapping features of cognitive dysfunction, headaches, and mood disorder. Isolated mood disorders such as depression are uncommon in pSLE. CNS vasculitis in pSLE more commonly affects the small vessels. Angiography-positive disease and strokes are uncommon. Transverse myelitis is an uncommon, serious manifestation of pSLE. Peripheral neuropathies are uncommon in children with lupus.

The diagnosis of NPSLE in children is based on clinical assessment including comprehensive neurocognitive testing, inflammatory markers, and neuroimaging. Children with neuropsychiatric disease commonly have...
antiphospholipid antibodies, in particular anti-β2-glycoprotein I (anti-β2GPI). A positive lupus anticoagu-
ant is often detectable in children with cerebrovascular disease including sinus vein thrombosis (SVT) and chorea. Neuroimaging demonstrates only subtle abnormalities in half of patients including the majority of children present-
ing with psychosis.

Hematologic disease is common in pSLE and affects a quarter of children. Treatment-refractory idiopathic throm-
boctytenic purpura (ITP) or severe autoimmune hemo-
ytic anemia can be the presenting features of pSLE. A
positive ANA and older age were found to be risk factors 
of pSLE in ITP. Serositis including pleuritis, pericarditis, and less commonly peritonitis affects about 20% of children 
with pSLE. Chest pain is the most common presenting 
feature. Inflammatory lung lesions including capillaritis and alveolar hemorrhage are uncommon. Although cardiomeg-
aly due to pericarditis and arrhythmia/conduction anomaly 
occur frequently, myocarditis and coronary arteritis are 
serious yet uncommon lupus features in children. The 
most common gastrointestinal (GI) manifestation of pSLE 
is lupus hepatitis. Inflammatory bowel manifestations are 
are. Overall atypical presentations can be found in up to a 
quarter of children ultimately diagnosed with pSLE and, 
when present, were found to correlate with poor outcome. Endocrinopathies of pSLE include hypothyroidism or hyper-
thyroidism and diabetes mellitus. Menstrual cycle distur-
bances and transient amenorrhea are common in girls with 
pSLE and may be associated with pituitary dysfunction or 
treatment with cyclophosphamide, leading to a decreased 
progesterone production.

**Diagnosis and Diagnostic Tests**

The diagnosis of pSLE is based on clinical findings, labora-
tory test results including inflammatory markers, comple-
ment levels, markers of organ involvement, and specific 
autoantibodies. Tissue biopsies and imaging studies can 
 further support and/or classify pSLE subtypes. The presence 
of 4 of 11 ACR classification criteria was found to have 
sensitivity of 96% and a specificity of 100%. A careful 
evaluation of potential organ involvement of pSLE is 
mandatory. Characteristic abnormal laboratory markers of active 
pSLE may include a raised erythrocyte sedimentation rate 
(ESR), anemia, which may be Coombs positive and hemo-
ytic, a low white blood count with predominant lympho-
 penia, low platelets, and low C3 and/or C4 complement 
levels. Paradoxically, the C-reactive protein (CRP) is 
normal in the vast majority of children with active lupus, except for those presenting with serositis or concurrent infections. An abnormal urinalysis including microscopic 
evidence of casts indicated renal involvement. Renal func-
tion impairment is best evaluated by serum creatinine, albumin, and urine protein-to-creatinine ratio. Lupus anti-
coagulant and specific lupus autoantibody testing including 
ANA, dsDNA, ENA, and antiphospholipid antibodies is 
mandatory. ANA is found is almost every child with pSLE, 
while dsDNA is detected in more than 80%. Novel 
antibodies have been proposed and require prospective vali-
dation in pSLE. Children may have frank hypothyroidism or 
hyperthyroidism or solely raised titers of thyroid 
antibodies.

**Immunosuppression**

The choice and dosing of immunosuppressive therapy 
regimen must be tailored to the extent and severity of the 
child’s organ disease. A thorough diagnostic evaluation is 
mandatory before initiating therapy. Immunosuppressive 
treatment protocols are commonly adopted from adult trials 
and meta-analyses. Treatment response criteria for pSLE 
were recently developed and validated.

Corticosteroids are the mainstay of lupus therapy. The 
general approach for major organ disease includes initial 
high-dose treatment with 2 mg/kg prednisone equivalent in 
two to three divided doses followed by a slow taper. This 
includes treatment of proliferative lupus nephritis, neuro-
sychiatric lupus except for chorea and SVT, myocarditis, 
and lung disease. Pulse intravenous (IV) methylprednisolone 
is frequently used for emergent situations including 
acute psychosis, MAS, and myocarditis. Arthritis, serositis, 
nonproliferative lupus nephritis, and mucocutaneous disease 
may require smaller initial doses of corticosteroids. The 
erythocytic of corticosteroids in pSLE is well established. 
However, the significant toxicity limits its long-term use at 
high doses. Short-term side effects include weight gain, 
sleep disturbances, emotional instability, increased hair 
growth, and impaired glucose metabolism. Long-term effects
include cataracts, growth arrest, vertebral fractures, and avascular necrosis. Combination immunosuppressive regimens are commonly used in children with major organ involvement. Cyclophosphamide, mycophenolate mofetil (MMF), and azathioprine have been studied in observational cohorts of pSLE patients. IV cyclophosphamide was considered the gold standard for severe organ disease such as proliferative lupus nephritis and neuropsychiatric disease. In accordance to adult SLE protocols, cyclophosphamide is commonly used for induction over 6 months, followed by either azathioprine or MMF. Induction therapy with MMF was found to be safe, well tolerated, and effective in a small cohort of renal and nonrenal pSLE patients. Complete renal remission is achieved in 40% to 50% of children at 6 months and 75% at 12 months. Commonly reported side effects that led to discontinuation of MMF therapy included severe diarrhea and abdominal pain. In children, optimal dosing may require pharmacokinetic evaluation on a stable dose. Efficacy and safety of MMF as maintenance drug is well established in pSLE. Induction therapy with azathioprine was found to be equally efficacious as cyclophosphamide in children with proliferative lupus nephritis and renal failure. Azathioprine has a good efficacy and safety profile. Routine monitoring of blood counts and liver function is required. Significant toxicity may occur in children with mutations in the gene encoding thiopurine methyltransferase or thiopurine S-methyltransferase (TPMT); however, the role of genotyping remains controversial. Azathioprine is also used as a maintenance drug following induction with cyclophosphamide.

Dialysis is required in children with end-stage renal disease. Plasmapheresis is indicated for specific disease manifestations such as thrombotic-thrombocytopenic purpura (TTP), transverse myelitis, and steroid-resistant nephritis. B cell depletion with the anti-CD20 antibody rituximab is the main biologic therapy currently used in pSLE. It was shown to be effective as a single agent in hematologic disease and in addition to standard therapy in refractory, difficult-to-treat pSLE. The safety profile remains to be systematically studied in pSLE. Autologous stem cell transplantation is rarely performed in pSLE.

MAS therapy in pSLE may include IV immunoglobulin, IV methylprednisolone pulse therapy, cyclosporine, or even chemotherapy according to HLH protocol.

**Antimalarials**

Antimalarials are strongly recommended for children and adults with SLE. On the basis of predominantly adult studies and meta-analysis, antimalarials are thought to decrease overall mortality and improve long-term outcome, modify lipid profiles, and control joint and skin disease, in particular discoid lupus lesions.

**Adjunctive Therapy**

Supportive medical therapies include angiotensin-converting inhibitors for renal protection and hypertension, contraception when applicable, organ dysfunction therapies including anticonvulsants and antipsychotic medication, and anticoagulation when applicable. High-factor sun sensitization due to chronic UV exposure is discussed. Education on sun safety is important, including regular use of sunscreen for sunburn protection. Educational efforts have to include disease and treatment, medication side effects, infection risk, and impact on social life and school.

Vitamin D is known to be a strong factor of bone protection in pSLE. Sufficient vitamin D doses in addition to calcium intake and physical activity are required to maintain good bone health. More recently a novel role of vitamin D in maintaining immune homeostasis was recognized. This is supported by studies demonstrating an inverse correlation between vitamin D levels and disease activity, in particular in overweight children with pSLE.

**Outcome**

Lupus in children and adults is a relapsing/remitting disease. The burden of pSLE is complex to determine because many factors such as access to health care, individual patient characteristics, disease activity, confounding diseases such as infections, and responsiveness to treatment all contribute to overall mortality and morbidity.

The overall mortality as captured by standard mortality rate (SMR) for all SLE in the United States between 1992 and 2001 was 3.06 deaths per million inhabitants per year, in Brazil between 1985 and 2004 it was 3.8 (2601 deaths, 90% female), and in Denmark it was 4.6. With improved therapies, mortality rates were shown to decrease in Canada (SMR, 10.1 in 1970-1977; 4.8 in 1978-1985, and 3.3 in 1986-1994). When comparing childhood- with adult-onset SLE, childhood-onset SLE was found to be independently associated with an increased mortality risk (hazard ratio [HR], 3.1), as was low socioeconomic status measured by education (HR, 1.9), and end-stage renal disease (HR, 2.1).

Young age at disease onset was repeatedly shown to be a predictor of adverse outcome. Children with pSLE in poor countries clearly have a higher mortality: In a small study from Nigeria the mortality was 30%. The Latin American LUMINA cohort had an 81% survival at last follow-up, the recent 5-year patient survival rate in Iran was 82.5%, and in Canada it was 100%. Infections continue to be the main cause of death in developing countries with limited access to health care. Nephritis has been consistently identified as a predictor of poor outcome in pSLE. Histologic subtype of proliferative disease, evidence of disease relapse, certain ethnicities, and poor response to therapy were strong predictors of end-stage renal disease in pSLE. Gibson demonstrated that treatment resistance portended a high risk of end-stage kidney disease and disproportionately affected African-American children with lupus nephritis.

Children with pSLE accrue disease- and treatment-related damage as captured in the domains of the Systemic Lupus International Collaborative Clinics (SLICC) Damage Index (see Chapter 80), constantly adding to the overall disease burden. Osteoporosis, cataracts, and osteonecrosis/avascular necrosis (AVN) are the leading domains of damage accrual. Individual patient characteristics, disease activity, corticosteroid therapy, calcium/vitamin D deficiency, and immobility contribute to impaired bone health in pSLE. AVN occurs in 6% to 10% of pSLE patients overall and is associated with corticosteroid therapy.
recently observed the complete absence of AVN in children younger than 14 years of age and suggested that age at the time of the initial corticosteroid therapy affects AVN occurrence. Neurocognitive deficits secondary to disease and treatment are increasingly recognized and significantly affect school performance and overall health-related quality of life.115,116 Early cardiovascular events including myocardial infarctions and strokes have become a major cause of morbidity and mortality.1

Drug-Induced Lupus Erythematosus

Several medications can cause systemic and subacute or chronic cutaneous lupus phenotypes in children.117 The cutaneous manifestations of systemic drug-induced lupus (DIL) include malar rash, purpura, erythema nodosum, urticaria, and photosensitivity. Systemic symptoms include arthritis, oral ulcers, pleuritis, hematologic manifestations, and less commonly renal disease. Characteristic laboratory findings of DIL are positive ANA and antihistone antibodies. Drugs implicated are minocycline, anticonvulsive drugs, hydralazine, procainamide, and isoniazid.118

Management of drug-induced lupus is based on the withdrawal of the offending drug. Topical and/or systemic corticosteroids and other immunosuppressive agents may be required in resistant cases.

Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is an acquired disease of the newborn caused by placental transfer of maternal anti-SSA/Ro and anti-SSB/La IgG antibodies. These can be present in mothers with SLE, Sjögren’s syndrome, and other autoimmune connective disorders, as well as clinically healthy women. Antibody transfer can lead to inflammation of the cardiac conducting system and subsequent fibrosis resulting in congenital heart block (CHB), which may be detected as early as 20 weeks of gestation. A prolonged PR interval is the first electrocardiographic sign of conduction system abnormality in NLE. The degree of heart block can vary, and rapid clinical progression from normal sinus rhythm to complete CHB over 2 weeks may be observed, causing life-threatening cardiomyopathy and fetal hydrops in the most severe cases. Isolated endocardial fibroelastosis can be found in some infants.119 Interestingly, infants with prenatal exposure to high-titer anti-SSB/La antibody levels are more likely to have noncardiac features of NLE, whereas cardiac disease tends to be associated with moderate or high maternal anti-SSA/Ro levels, independent of anti-SSB/La titers in CHB.120 The overall risk of CHB in anti-SSA/Ro–positive women is estimated to be 2% to 5%,120 but this risk may be increased by 10-fold in women with a previous child with CHB.121 A recent study suggests an overall recurrence rate of cardiac NLE of 17%, independent of maternal health, antenatal use of steroids, antibody status, severity of cardiac disease in the first affected child, or sex of the subsequent child.122

In addition to heart block, newborns with NLE can present with a characteristic NLE rash, hepatic dysfunction, and hematologic abnormalities including significant thrombocytopenia. Typically the NLE rash is located around the eyes but may present elsewhere on the body.123 Hepatobiliary disease can have three distinct presentations: (1) transient conjugated hyperbilirubinemia with mildly raised liver function tests (LFTs) in the first weeks of life; (2) mild elevations of LFTs at 2 to 3 months of life; and (3) severe liver failure during gestation or in the neonatal period.124 NLE neurologic involvement can include magnetic resonance imaging (MRI) findings of nonspecific white matter changes and calcification of the basal ganglia. NLE “vasculopathy” is reported. Recently, an association of NLE and hydrocephalus has been recognized.125 Chondrodysplasia punctata, a stippling of the epiphyses, and pulmonary capillaritis are rare clinical presentations of NLE.123,126

In a prospective multicenter study of 128 infants whose mothers had been referred for the presence of anti-SSA/Ro antibodies, regardless of their diagnosis, hematologic abnormalities and raised liver enzymes were seen in 27% and 26%, respectively.127 Cutaneous NLE manifestations were present in 16%. Only 2 of the 128 infants (1.6%) presented with complete CHB. In a recent Japanese review, 193 infants with NLE were described reporting CHB in 23%.128

Treatment of CHB in NLE remains controversial. Prevention of progression to complete CHB may be achieved by treating the mother with fluorinated steroids (dexamethasone or betamethasone), which are not metabolized by the placenta and are available to the fetus in an active form. IV immunoglobulin had been used to prevent the development of CHB in the index patient and in subsequent pregnancies.129 The current recommendation is to screen anti-Ro/SSA antibody–positive mothers with serial echocardiograms and obstetric sonograms biweekly starting from week 16 of gestation. Early detection of cardiac manifestations of NLE including premature atrial contractions or moderate pericardial effusion preceding CHB may potentially be targeted with preventive therapy.129,130 First-degree heart blocks can be reversed by dexamethasone treatment of the mother.131 Once third-degree block is unequivocally identified, reversal is unlikely to be achieved. The majority of children with CHB require pacemakers.121

The treatment approach to extracardiac manifestations of NLE is conservative. Skin disease may require topical corticosteroids and sun protection.133 Transient elevations of LFTs and cytopenias commonly do not require therapy.124

The morbidity of cardiac neonatal lupus is estimated to be 20%.121 Mortality is particularly high in patients with CHB and concurrent cardiomyopathy. Children with NLE can develop SLE later in life. Concerns of potential long-term neurocognitive deficits of NLE patients need further evaluation.134

JUVENILE DERMATOMYOSITIS

Definition and Criteria

Juvenile dermatomyositis (JDM) is an inflammatory, immune-mediated vasculopathy with predominant involvement of muscle and skin that may involve other organs as well. JDM is by far the most common form of idiopathic inflammatory myopathy (IIM) in children and adolescents; therefore other types (such as juvenile polymyositis) are not addressed in this chapter.
Epidemiology

The incidence of JDM has been reported at approximately two to three cases per million children\textsuperscript{135,137} with a mean age of onset of JDM of 6 to 9 years of age.\textsuperscript{136,138-141} JDM may begin before 4 years of age in approximately 25\% of cases.\textsuperscript{136,138-141} Females are affected more commonly than males in a ratio of approximately 2:1.\textsuperscript{136,138-141} Birth distributions for some subgroups of JDM patients have been noted and suggest that perinatal exposures may influence the onset of disease.\textsuperscript{142}

Genetics, Etiology, and Pathogenesis

It is thought that JDM is an autoimmune disorder in which environmental factors trigger an immune vasculopathy in genetically susceptible individuals. There is circumstantial evidence supporting the possible role of infection in the pathogenesis of JDM.\textsuperscript{139,143} Gene expression profiling in newly diagnosed JDM patients demonstrated interferon signature patterns in affected muscle tissue, suggesting preceding viral infection.\textsuperscript{144} Electron microscopic studies of affected muscle demonstrate tubuloreticular inclusions, which can also indicate a type I interferon response. Many different infections have been associated with JDM.

Both human leukocyte antigen (HLA) and non-HLA genetic relationships have been reported to be disease associated or protective. In Caucasians, the HLA allele HLA DRB1*0301 is the strongest HLA risk factor (odds ratio [OR], 3.9). The HLA associations do not seem to affect disease course or complications.\textsuperscript{147} Similarly, the presence of polymorphisms of cytokine genes may confer an increased risk on the development of JDM or may be protective.\textsuperscript{146} Polymorphisms at these and other alleles may also be associated with disease complications and course.

The central events of the immune angiopathy of JDM include an overexpression of major histocompatibility complex (MHC) type I molecules on the surface of myofibers and a type I interferon response.\textsuperscript{147} An immune complex–mediated vasculopathy with the presence of the C5-9 membrane attack complex, as well as immunoglobulins and C3 complement with complement activation, is evident. There is also a perivascular and perimysial infiltration of plasmacytid dendritic cells, leading eventually to infiltration by CD4\(^+\) T cells, B cells, macrophages, proinflammatory cytokines, and chemokines. This leads to vascular damage, capillary dropout, and muscle ischemia. Upregulation of MHC class I molecules on myofibers is associated with the activation of nuclear factor κB (NFκB), which can lead to muscle damage. Maternal microchimerism has been noted in the majority of patients with JDM and in frequencies much greater than siblings or healthy controls,\textsuperscript{137} suggesting that mechanisms similar to graft-versus-host disease may also play a role in the pathogenesis of JDM.

**Clinical Features**

Patients usually present with an insidious onset of fatigue, decreased functional ability, stiffness, and weakness. Irritability may result from muscle pain and an inability to participate in routine activities, especially in young children. A more acute onset, with fever, may occur in about half of patients. Weakness with rash is the presenting problem in about 50\% of cases, weakness alone in about 25\%, and the remainder present with predominantly skin symptoms. The clinical features at presentation are shown in Table 108-2.\textsuperscript{136,140,148-151}

Symmetric proximal muscle weakness typically presents first in the lower extremities, manifesting as difficulty climbing stairs and running. Patients may demonstrate a Gower sign reflecting weakness of the lower limb and trunk muscles. Reaching for objects above the head and hair brushing are difficult because of weakness of the shoulder girdle. An increased lumbar lordosis results from weakness of the trunk muscles, which also makes it difficult to roll in bed and get out of bed. Neck flexor weakness makes it difficult to hold the head upright. The muscles may be painful and tender to touch due to edema. Weakness of the distal musculature is unusual but may be present late in disease. Weakness of the palatal musculature results in dysphonia, dysphagia, and nasal regurgitation.\textsuperscript{152} Rarely, patients may be so weak as to be bedbound.

Skin rashes are present in approximately 75\% of patients at presentation. Rash may be the presenting feature and in fact the only symptom (clinically amyopathic dermatomyositis), although subtle abnormalities may be detected on muscle MRI. Some skin features are predictive of poor outcome such as calcinosis and severe nail-fold capillary abnormalities.

The cutaneous features of JDM have been well summarized in a comprehensive review.\textsuperscript{153} It is important to note that activity of the skin disease frequently does not correlate with activity of the muscle disease, and cutaneous abnormalities may have a significant impact on the patient's quality of life.

Gottron papules occur over the extensor surfaces of the metacarpophalangeal (MCP) and interphalangeal (IP) joints, as well as the knees, elbows, and medial malleoli (Figure 108-3A). They are erythematous to violaceous papules and may have associated scaling, crusting, erosions, ulcerations, or pigmented change. This is differentiated from Gottron sign, which involves macular lesions occurring in the same distribution.

The pathognomonic heliotrope rash consists of violaceous to erythematous discrete or confluent macules confined to the upper eyelids (Figure 108-3B). This can extend periorbitally and often presents with generalized periorbital edema with discoloration.

Other cutaneous lesions include erythematous lesions in both sun-exposed and non-sun-exposed areas. Common

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>% Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal muscle weakness</td>
<td>82-100</td>
</tr>
<tr>
<td>Characteristic rash (Gottron papule ± heliotrope)</td>
<td>66-95</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>5-30</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>18-44</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5-43</td>
</tr>
<tr>
<td>Arthritis</td>
<td>23-61</td>
</tr>
</tbody>
</table>
Calcinosis cutis can occur in up to 40% of patients with JDM; occasionally it may be present at the time of diagnosis. It is a dystrophic calcification and occurs more often in patients who have been “under-treated” or had a delay in the start of treatment. Calcinosis may take several forms: superficial plaques and nodules; tumoral; fascial plane deposition; and an exoskeleton (Figure 108-4A,D). Patients may have more than one pattern. The superficial lesions are often subject to minor trauma and can lead to skin breakdown. They may also extrude a chalklike material (see Figure 108-4A). Tumoral deposits can impair function and lead to skin breakdown, especially when they involve flexural areas. Occasionally the calcinosis in these areas leads to an intense inflammatory reaction resembling cellulitis. Fascial plane calcinosis may impair function when crossing joint lines (see Figure 108-4B). An exoskeleton may give a scleroderma-like picture. Contrary to old beliefs that calcinosis was purely a healing process indicating that JDM was inactive, these lesions are often associated with ongoing active disease requiring more aggressive systemic treatment.

Lipodystrophy is a late manifestation reported in up to 40% of patients, developing a median of 4.6 years after diagnosis.\textsuperscript{154} It may be localized, partial, or generalized and frequently occurs with metabolic syndrome, which includes hyperglycemia, hypertriglyceridemia, insulin resistance, hepatomegaly, transaminisits, and premature organ failure. Acanthosis nigricans may occur as well.

Vasculopathy is the characteristic pathologic feature of JDM. Cutaneous manifestations of vasculopathy include livedo reticularis and ulceration (Figure 108-3D). Ulcerative lesions are more common over extensor surfaces and the inner canthi of the eye. Erythema and capillary dilatation of the gingiva are a part of the vasculopathic manifestations. Capillary nail-fold changes are a major manifestation of JDM and are often visible to the naked eye. These are best observed under a microscope, but excellent resolution may be obtained by placing a drop of oil or water at the nail bed and magnifying this with a dermatoscope, otoscope, or ophthalmoscope at plus 40 diopters (Figure 108-3C). Characteristic changes include dilatation of the vessels, tortuosity, bushy capillaries, dropout, hemorrhage, and thrombosis. The severity of the capillary change may reflect the degree of disease activity and may also correlate with damage.

Areas of involvement include the cheeks, the shawl area of the shoulders, and the “V” area of the lower anterior neck and chest wall. As opposed to SLE, the malar rash of JDM often involves the nasolabial folds and may involve the chin and forehead as well. Both the shawl sign and “V” rash are associated with anti-synthetase antibodies. Linear erythematous lesions may occur over extensor surfaces including the tendons of the hands and feet.

Figure 108-3  Fifteen-year-old boy with newly diagnosed juvenile dermatomyositis demonstrating Gottron papules over the metacarpophalangeal and proximal interphalangeal joints (A), heliotrope rash with periorbital swelling (B), and nail-fold capillary dropout, dilatation, and tortuosity (C). D shows a 4-year-old boy with juvenile dermatomyositis with a cutaneous ulcer adjacent to his right axilla. He died 3 months after presentation.
GI manifestations include dysphagia from both palatal muscle weakness and involvement of the distal esophagus. Intestinal vasculopathy can result in diffuse abdominal pain, lower GI bleeding, or bowel perforation with peritoneal free air.

Arthritis occurred in 61% of patients in one cohort, reported a median of 4.5 months after the JDM onset. Osteopenia may result from disuse and treatment, and pathologic fractures may develop. Rhabdomyolysis is a rare complication that may follow infection.

Multiple respiratory manifestations may occur and are often subclinical. In one large case series followed for a mean of 16.8 years, a low total lung capacity (TLC) was found in about 25% and a low diffusing capacity for carbon monoxide.
monoxide (DLco) in about 50% of patients. Just over one-third of patients had abnormalities on high-resolution computed tomography (CT) scanning such as interstitial lung disease, chest wall calcinosis, and airway disease. Spontaneous pneumothorax has been reported.

Cardiac manifestations are uncommon and can include pericarditis, myocarditis, and arrhythmias. However, subclinical left ventricular diastolic dysfunction, systolic hypertension, and electrocardiogram abnormalities occurred in 22% of one series of patients and were associated with cumulative organ damage. Hypertension is usually associated with high-dose glucocorticoid therapy.

The association with malignancy is limited to case reports such that a search for malignancy is not required in children with JDM.

**Disease Monitoring**

Muscle enzyme levels are frequently normal soon after treatment and are therefore unreliable indicators of disease activity. Several tools have been developed and validated to monitor the course and outcome of children with JDM. These include the 0- to 10-point Manual Muscle Test, the Childhood Health Assessment Questionnaire (CHAQ), the Childhood Myositis Assessment Scale (CMAS), the Disease Activity Score (DAS), the Myositis Damage Index (MDI), and the Intention to Treat Index (MITAX). The Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) consists of a series of 10 visual analogue scales in different organ systems. In 2008 a prospective validation study of a core set for the evaluation of response to therapy in JDM was published under the auspices of the Paediatric Rheumatology International Trials Organization, the ACR, and the European League Against Rheumatism (EULAR) (Table 108-3). Provisional criteria for the evaluation of response to therapy in JDM include at least 20% improvement from baseline in three of six core set variables with no more than one of the remaining worsening by more than 30%, which cannot be muscle strength. The Cutaneous Assessment Tool has undergone preliminary validation in a series of 113 children with JDM. It measures both skin activity and skin damage.

**Diagnosis and Diagnostic Tests**

The diagnostic criteria published by Bohan and Peter require that patients have a characteristic skin rash plus three of the following four to meet the definition of “definite” JDM: symmetric proximal muscle weakness, elevated serum levels of muscle-derived enzymes, myopathic electromyogram (EMG), and histologic evidence of myositis. Patients with rash and two of these four criteria may be diagnosed with “probable” JDM. Because both EMG and biopsy are invasive procedures, many practitioners now rely on MRI studies of muscle to support the diagnosis (see later).

Laboratory evaluation in children with JDM helps to support the diagnosis and exclude other causes of muscle weakness. Systemic markers of inflammation such as the ESR and CRP generally reflect the degree of disease activity. Serum levels of neopterin and elevated levels of CD19 B lymphocytes have been suggested as good markers of disease activity, as has von Willebrand factor.

Elevated serum levels of muscle enzymes form one of the diagnostic criteria of JDM. Measurements of creatine kinase, lactate dehydrogenase, aspartate transaminase, and aldolase should all be obtained. However, their degree of elevation does not necessarily correlate with active disease and they can occasionally be normal, even at presentation, particularly with long-standing disease. Serum levels of muscle enzymes drop dramatically with treatment, often before a clinical improvement is seen.

Electromyography has generally fallen out of favor despite still being part of the diagnostic criteria, especially if MRI is available. Characteristic EMG changes include spontaneous fibrillations, increased insertional activity, decreased amplitude, and duration of action potentials.

Although abnormal muscle biopsy is one of the criteria proposed by Bohan and Peter in the diagnostic criteria for juvenile dermatomyositis, many clinicians elect not to do muscle biopsies when patients present with classic clinical features of JDM. This is because the procedure is invasive, painful, may not add to the diagnostic accuracy in individual patients, and may be normal in up to 20% of patients. Normal results may occur because of sampling error or patchy muscle involvement. Better yield might be afforded through the use of MRI to determine best sites for biopsy. Care should be taken not to biopsy a site that has previously undergone electromyography.

The characteristic light microscopic features are suggestive of an inflammatory vasculopathy. This includes endothelial cell swelling, capillary dropout with a reduced capillary-to–muscle fiber ratio, microthrombosis, and infarction. There is a relatively sparse inflammatory infiltrate consisting mainly of T cells, but there may be myeloid cells present as well. Muscle fibers demonstrate perifascicular atrophy, overexpression of class I major histocompatibility complex, deposition of immunoglobulin, and the membrane attack complex C5-9. There are also areas of degenerating and regenerating muscle fibers. Chronic

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**Table 108-3 Domains and Suggested Variables Included in the Final Core Set for the Evaluation of Response to Therapy in Juvenile Dermatomyositis (JDM)**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Suggested Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s global assessment of patient’s overall disease activity</td>
<td>10-cm VAS</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>CMAS (or MMT)</td>
</tr>
<tr>
<td>Global JDM disease activity tool</td>
<td>DAS (or MYOACT or MITAX)</td>
</tr>
<tr>
<td>Parent’s global assessment of patient’s overall well-being</td>
<td>10-cm VAS</td>
</tr>
<tr>
<td>Functional ability assessment</td>
<td>CHAQ</td>
</tr>
<tr>
<td>Health-related quality of life assessment summary score</td>
<td>CHQ physical</td>
</tr>
</tbody>
</table>

CHAQ, Childhood Health Assessment Questionnaire; CHQ, Child Health Questionnaire; CMAS, Childhood Myositis Assessment Scale; MITAX, Myositis Intention to Treat Index; MMT, Manual Muscle Test; MYOACT, Myositis Disease Activity Assessment; VAS, Visual Analogue Scale.

changes include an increase in the perimysial and endomysial connective tissue, thought to reflect muscle fiber damage and loss. Histopathologic changes have been shown to correlate with both ulcerative disease and poor prognosis.172

Recently, an international group has developed a scoring system that can be used in routine laboratories. The scoring tool uses four domains to reflect the degree of pathology: inflammatory, vascular, muscle fiber, and connective tissue. It also includes a visual analogue scale from 0 to 10 to reflect overall damage.173

Currently the diagnosis of JDM is made on the basis of Bohan and Peter criteria. However, many pediatric rheumatologists now have turned to MRI to assist with the diagnosis and avoid more invasive tests such as EMG and muscle biopsy.174 Inflammation characteristic of JDM is seen as high-signal intensity on fat-suppressed weighted and short tau inversion recovery (STIR) images.175 STIR sequences can also reveal fascitis and panniculitis. Muscle atrophy is best appreciated on T1-weighted sequences as increased signal between muscle planes. An increase in mean T2 relaxation time correlates with increased muscle disease activity and muscle strength.176

ANA positivity is seen in 10% to 85% of patients with JDM. Myositis-associated (MAA) and myositis-specific antibodies (MSA) are uncommon unless the JDM is part of an overlap syndrome.177,178 In those patients who are positive for MAAs and MSAs (anti–signal-recognition particle, anti-synthetase, and anti-Mi2), the clinical associations are the same as in adult disease. The newly described autoantibody anti-p155/140 has been identified in up to 29% of one series of JDM patients, and anti-p140 has been identified in 23% of JDM patients, associated with calcinosis in one series.180

Differential Diagnosis

The most important differential diagnosis for patients presenting with rash and muscle weakness is SLE, particularly for those patients presenting with significant arthritis and a malar rash. Characteristic autoantibodies of SLE, cytopneas, renal disease, and hypocomplementemia help to differentiate these disorders. Patients with systemic sclerosis and prominent myositis may be difficult to differentiate from patients with JDM. Patients with mixed connective tissue disease and other overlap syndromes may have features of JDM in addition to those of other autoimmune connective tissue diseases.

Other idiopathic inflammatory myopathies are extremely rare in children. These include inclusion body myositis, granulomatous myositis, and macrophagic myositis.

Patients who present with either no rash or mild rash and predominant muscle weakness may need to be differentiated from patients with primary myopathies. Patients with muscular dystrophies often have positive family histories and an insidious onset of disease with characteristic muscle groups involved. Congenital myopathies usually present in infancy with hypotonia. Metabolic myopathies may be associated with developmental delay. Cramping and weakness after exertion may also be signs of metabolic myopathy.

Various infections may lead to an acute myositis. Perhaps the best recognized is influenza B, presenting with acute calf pain, weakness, and raised muscle enzyme levels. Trichinella infection may be associated with periorbital edema and significant peripheral eosinophilia. Many other bacteria, viruses, and parasites may cause myositis; they should be suspected in the appropriate clinical circumstance.

Treatment

The management of patients with JDM requires a multidisciplinary team approach with medical specialists (rheumatologists, dermatologists, neurologists); nurses; rehabilitation specialists; social workers; and nutrition specialists.

Early aggressive treatment has been shown to result in better long-term outcomes and prevent disease-related complications.139,141,181,182 The cornerstone of treatment is high-dose, daily corticosteroid, usually combined with a second-line agent, typically methotrexate (MTX). Some practitioners advise the early use of high-dose, IV pulse methylprednisolone to ensure appropriate absorption when there may be a concern of intestinal vasculitis,183 when there is a flare of disease, or when a patient seems unresponsive to standard steroid therapy. The usual course has been to start at 2 mg/kg/day in one to three divided doses and to begin to taper when muscle enzymes have normalized and strength has improved, with a subsequent slow taper over 18 to 24 months in uncomplicated cases. With steroid treatment alone, a significant number of patients do not respond fully and have complications, and some patients may be overtreated and have steroid-related complications. As a result, other agents are commonly prescribed.

MTX has been used for decades in children with steroid-resistant JDM and has recently been incorporated into many treatment protocols. In addition to its anti-inflammatory effect, it allows for a lower cumulative dose of corticosteroids.184 A recent survey of North American pediatric rheumatologists documented that the most common treatment approach to patients with JDM is a combination of prednisone and MTX.185

In patients who do not respond adequately, there are several options. IV immunoglobulin (IVIG) has been shown in a randomized controlled trial in adults with dermatomyositis to be effective,186 as well as in case series in childhood JDM.187 Several different protocols have been described. Generally, if there is no improvement within 2 months, it is unlikely that additional IVIG will be effective.

Mycophenolate mofetil at an initial dose of 20 mg/kg in two divided doses was studied in 30 patients who had not responded to prednisone and MTX.188 A significant improvement in muscle and skin DAS was noted at 12 months, with a significant reduction on steroid dose and no serious adverse events. There was an increase in mean height and weight as well.

Cyclosporine A is used frequently in Europe as a second-line agent with good results.189 A trial is currently under way in Europe for newly diagnosed patients with JDM comparing prednisone alone with prednisone plus MTX with prednisone plus cyclosporine A.

Cyclophosphamide has generally been reserved for patients with treatment-resistant disease, severe ulcerative disease, or lung involvement. Major clinical benefit was
noted in a small cohort of patients without serious toxicity.\(^{190}\)

The results with anti–tumor necrosis factor (TNF) treatment with both etanercept and infliximab have been reported in several small case series, with both positive and negative outcomes.\(^{191}\) There are reports of several cases of myositis developing while on etanercept treatment. The use of rituximab has been reported in only a small number of patients with good results.\(^{192}\) The results of the rituximab in myositis trial are awaited. Nevertheless, a trial may be warranted in patients with severe unresponsive disease. It is possible that patients who have myositis-specific autoantibodies would respond better. A few patients have undergone successful autologous stem cell transplantation.\(^{193}\)

One approach to the treatment of patients with JDM has been to use a step-wise addition of medications if patients fail to improve according to a predetermined outcome (similar to “treat-to-target” approach in rheumatoid arthritis). Using this approach, Kim and colleagues\(^{192}\) reported excellent outcomes in a series of patients who were treated, progressively, with prednisone (98%), MTX (78%), IV methylprednisolone (84%), cyclosporine A (27%), IVIG (22%), plasma exchange (8%), and cyclophosphamide (4%).

Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), using consensus building techniques, proposed three protocols for the treatment of moderately severe JDM. All include corticosteroids in one to two doses per day (maximum 60 mg) plus MTX, preferably given by the subcutaneous route at the lower dose. Clinicians may also add either pulse steroids or IVIG of 15 mg/m\(^2\) or 1 mg/kg, maximum 40 mg/wk.\(^{194}\) One approach to the pharmacologic management of JDM is listed in Table 108-4.

**Table 108-4  An Approach to the Management of a Patient with Juvenile Dermatomyositis**

<table>
<thead>
<tr>
<th>For Muscle Weakness</th>
<th>Initial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Methotrexate subcutaneously</td>
</tr>
<tr>
<td>If Failure to Respond to Initial Treatment, Consider Adding:</td>
<td>IV pulse methylprednisolone</td>
</tr>
<tr>
<td>If Failure to Respond to Second-Line Treatment, Consider Adding:</td>
<td>Cyclophosphamide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For Skin</th>
<th>Initial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration</td>
<td>Sun protection</td>
</tr>
<tr>
<td>If Failure to Respond to Second-Line Treatment, Consider Adding:</td>
<td>Hydroxychloroquine</td>
</tr>
</tbody>
</table>

\(^{IV}\), intravenous; \(^{IVIG}\), intravenous immunoglobulin.

**Outcome**

In the precorticosteroid era, approximately one-third of patients with JDM went into a complete clinical remission, one-third had a chronic course, and one-third died.\(^{197}\) Advances in medical therapy, earlier diagnosis, and more aggressive treatment protocols have led to significantly improved outcomes; however, there is still significant morbidity and a small mortality associated. Current mortality is less than 5%.\(^{198,199}\)

Patients may follow one of three disease courses: monophasic, polycyclic (flares of disease while off treatment), or chronic continuous courses. Delayed recognition of disease and initial undertreatment may result in more prolonged disease course. In the “modern era,” two large series showed that approximately 40% of patients pursued a monophasic course and the remainder had either a polycyclic or a chronic continuous course.\(^{141,199}\) Using an aggressive early stepwise treatment approach, only 4% had a chronic disease course, suggesting that early control of muscle inflammation prevents long-term morbidity.\(^{192}\)

The largest follow-up study included 490 patients from Europe and Latin America followed for a mean of 7.7 years seen between January 1980 and December 2004.\(^{140}\) Reduced muscle strength and/or endurance were documented in 40% to 50%, although it was severe in less than 10% of patients. Persistent disease activity was noted in 40% to 60%. Cumulative damage occurred in 70%, primarily cutaneous. Decreased functional ability was reported in 40% and major impairment in 7%. A chronic course was the strongest predictor of poor prognosis.

There are a number of factors considered to predict a poor outcome including a delay in treatment or...
SCLERODERMA

The scleroderma disorders in children can be classified into systemic, localized, and others (Table 108-5). The systemic scleroderma are rare in the pediatric age group and are outnumbered by the localized forms by approximately 10:1.

Systemic Sclerosis

Epidemiology

Juvenile systemic sclerosis (JSSc) makes up approximately 10% of all cases of systemic sclerosis (3); the incidence rate in a recent U.K. study was reported as 0.27 per million children. Females outnumber males anywhere from 4:1 to 10:1 (5). The incidence seems to increase with increasing age, although in one large multicenter review the mean age of onset was 8.1 years (22). Diffuse disease is much more common than limited disease. An increased family history of autoimmune disease including scleroderma has been noted in some series.

Little work on etiology and pathogenesis has been done specifically in juvenile systemic sclerosis, and it is assumed to be identical to adult disease. The interested reader is referred to Chapter 83.

Clinical Features

The onset of diffuse systemic sclerosis is often insidious, and delay in diagnosis ranged from a median of 1 to 2.8 years in three large series (20,21,30). The most common presenting features are Raynaud’s phenomenon, skin edema, and sclerodactyly (Table 108-6). The diagnosis should be considered susped in the absence of Raynaud’s phenomenon.

Although skin edema is the earliest cutaneous abnormality, it is followed fairly quickly by induration, sclerodactyly, and loss of facial creases.

Table 108-5 Classification of Scleroderma in Childhood

<table>
<thead>
<tr>
<th>Systemic Sclerosis</th>
<th>Diffuse</th>
<th>Overlap Syndromes</th>
<th>Localized Scleroderma*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Circumscribed morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Linear morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generalized morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pansclerotic morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mixed morphea</td>
</tr>
</tbody>
</table>

*Proposed Pavia criteria (23)

JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Table 108-6 Clinical Features at Diagnosis and during Course in 153 Patients with Juvenile Systemic Sclerosis from 55 Centers

<table>
<thead>
<tr>
<th>Feature</th>
<th>% At Diagnosis</th>
<th>% During Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>46</td>
<td>66</td>
</tr>
<tr>
<td>Skin induration</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Calcification</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Peripheral Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Digital infarcts</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Digital pitting</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Abnormal capillary microscopy</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Abnormal chest CT scan</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Reduced DLCO</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Reduced FVC</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis/arrhythmia</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Arthritis</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Tendon friction rubs</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Reflux</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised creatinine/proteinuria</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Renal crisis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal brain MRI</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.


Raynaud’s phenomenon involves the distal extremities and rarely other acral areas such as the earlobes and tip of the nose. Occasionally it may lead to digital infarcts resulting in pitting or more significant gangrenous change. Capillary nail-fold abnormalities, visible either to the naked eye or by capillary microscopy, have been reported in at least 50% of patients and include areas of dropout and abnormal capillaries with dilatation and tortuosity.

Abnormalities of the musculoskeletal system include mild inflammatory synovitis, which is nonerosive; joint contractures most commonly resulting from skin and subcutaneous tightness around the joints; and myositis. In patients with overlap syndromes the muscle involvement is
more significant. Otherwise scleroderma myositis is generally quite mild. Tendon friction rubs may be felt or heard in a minority of patients.

Involvement of the respiratory system has become the most significant cause of morbidity and mortality in patients with systemic sclerosis. Early changes may be documented by high-resolution computed tomography, although this may not offer much greater benefit than well-performed pulmonary function tests (PFTs). \textsuperscript{204} It is important to document the pulmonary status early in the disease process because it is only then, before irreversible fibrosis occurs, that reversal of abnormalities may be possible. Pulmonary function abnormalities include a reduced forced vital capacity, a reduced FEV\textsubscript{1}-to-forced vital capacity (FVC), and a reduced DL\textsubscript{CO}. Severe chest wall involvement with restriction of movement may also lead to abnormal PFTs. Early CT changes include a ground-glass appearance suggestive of alveolitis.\textsuperscript{205} Rarely, pleural effusions may occur. Cardiac involvement includes pericarditis (which may be asymptomatic), arrhythmia, and congestive heart failure (CHF). Pulmonary arterial hypertension may develop in the face of severe lung disease. Cardiac disease (resulting primarily from CHF) was the most common cause of mortality in one series of 135 patients with juvenile systemic sclerosis.\textsuperscript{206}

Involvement of the GI system is common with symptoms of dysphagia and gastroesophageal reflux. More diffuse involvement can lead to reduced GI motility with bacterial overgrowth resulting in malabsorption. Severe constipation may occasionally occur. Renal involvement is much less common in juvenile than adult scleroderma and can include proteinuria, hypertension, and the eventual development of renal crisis. Neurologic involvement is unusual but can include seizure, stroke, and peripheral neuropathy.

**Diagnosis and Diagnostic Tests**

The diagnosis of systemic sclerosis rests on the presenting signs and symptoms and the investigation of organs that may be affected by the process. Seventy-five to 97% of patients were antinuclear antibody positive in three series.\textsuperscript{200,201} Specific autoantibodies include antitopoisomerase in approximately 33%, anticientromere antibody in less than 10%, and autoantibodies associated with overlap syndromes (anti-PM-Scl, anti-U1-RNP, anti-Ro) in a smaller number depending on the series. Rheumatoid factor may be present in up to 20% of patients.

Skin biopsy is rarely performed. Pathologic findings include dense collagenization and loss of adnexal structures. An inflammatory infiltrate composed primarily of mononuclear and mast cells is seen early in the course.

It is important to investigate the various organ systems that may be involved by systemic sclerosis in order to help prognosticate and develop an appropriate management plan. Investigations should include, at a minimum, PFTs with a DL\textsubscript{CO}, an electrocardiogram, an echocardiogram, and a chest radiograph. For patients unable to perform PFTs, high-resolution CT scan is indicated. This is also indicated in patients with abnormal PFTs to detect early alveolitis. Serum KL-6 is a mucin-like glycoprotein strongly expressed in type II pneumocytes and may be a useful noninvasive marker of pulmonary fibrosis in children with JSSc.\textsuperscript{207}

It can be assumed that most patients have GI involvement and that an upper GI series will be abnormal. This test is indicated for patients with severe pain unresponsive to standard agents and severe dysphagia. Hydrogen breath test and measuring fat-soluble vitamins may be helpful in patients with suspected malabsorption. Radiographs of the hands may be helpful in showing distal acro-osteolysis in patients with severe Raynaud’s phenomenon and occasionally may show calcinosis.

When patients present with Raynaud’s phenomenon, capillary nail-fold abnormalities, and edematous or indurated skin, the diagnosis is clear and the differential diagnosis is limited. However, patients are often seen early in the course with just Raynaud’s phenomenon and a positive ANA. In those situations the most important differential diagnoses to consider are systemic lupus erythematosus, overlap syndrome/mixed connective tissue disease, and juvenile dermatomyositis. Although many other diseases are associated with skin fibrosis, they are not associated with the characteristic multisystem involvement as systemic sclerosis and should not pose a diagnostic challenge.

Provisional classification criteria have been developed and accepted by the Pediatric Rheumatology European Society (PReS), ACR, and EULAR on the basis of a Delphi survey and nominal group techniques.\textsuperscript{208} These were proposed because current criteria had not been studied in children and are not sensitive enough to detect early disease. Furthermore, they do not include key features of early disease such as Raynaud’s phenomenon and a positive ANA. In those situations the most important differential diagnoses to consider are systemic lupus erythematosus, overlap syndrome/mixed connective tissue disease, and juvenile dermatomyositis. Although many other diseases are associated with skin fibrosis, they are not associated with the characteristic multisystem involvement as systemic sclerosis and should not pose a diagnostic challenge.

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**Treatment**

The approach to the management of patients with systemic sclerosis should include treating the basic disease process itself, as well as the various organ manifestations. No controlled studies exist in children, and data must be extrapolated from the adult literature. The EULAR Scleroderma Trials and Research Group has made recommendations regarding management of patients with systemic sclerosis, and they should be considered for all patients.\textsuperscript{209} Because no specific treatment studies have been reported in children and adolescents, the reader is referred to Chapter 84 for a discussion of treatment where the same principles hold. It should be noted that for patients with rapidly progressive disease and progressive lung disease, autologous stem cell transplantation may provide the only opportunity for survival and has been successful in a number of patients with juvenile systemic sclerosis.\textsuperscript{210}

**Outcome**

Very little long-term outcome data are available for JSSc. Morbidity is substantial from the multisystem involvement with marked impact on the quality of life. The survival rates in juvenile systemic sclerosis are better than adult disease. Mortality in three large series varied from 12% to 30%.\textsuperscript{200,201,205} The most common causes of death include
cardiac (including pulmonary arterial hypertension) and respiratory failure. Factors considered to be significant predictors of mortality include fibrosis on chest radiograph, raised creatinine levels, and pericarditis, whereas a short disease duration at diagnosis may confer protection.211

Localized Scleroderma

Epidemiology

Localized scleroderma (LSc), also known as morphea, had a reported incidence of 2.7 per 100,000 of the general population in the Mayo Clinic series,212 and 3.4 per million children in the United Kingdom,213 making it much more common than systemic sclerosis in the pediatric age group. The female-to-male ratio is approximately 2:1, and the average age of onset is approximately 7 years. Mild lesions may never get to medical attention, so the incidence may be even higher. Congenital morphea has been reported.214 Several classification schemes have been developed; the proposed Pavia criteria are listed in Table 108-5.215

Linear lesions are more common in the pediatric age group.213,216,218

Etiology and Pathogenesis

Like systemic sclerosis, it is likely that environmental factors trigger immune activation leading ultimately to fibrosis. There have been no genetic studies to date to suggest that the HLA or non-HLA systems play a role, although those studies are under way. Familial occurrence is uncommon, but there is a strong family history of other autoimmune disorders.216,219 Trauma has been considered as a possible inciting feature.220 Borrelia infections have been implicated in Europe but not in North America. The presence of elevated levels of serum cytokines (such as TNF and interleukin [IL]-1) that may influence fibroblast proliferation provide strong evidence for the role of immune activation in disease pathogenesis.221 Microchimerism has been reported, and as with other connective tissue diseases it suggests that mechanisms similar to graft-versus-host disease also may play a role. Several drugs and toxins may lead to cutaneous fibrosis, although none has been consistently identified in patients with LSc.

Clinical Features

There is usually a delay in presentation of several months because the lesions themselves are typically not symptomatic. Active circumscribed (Figure 108-5A) and linear lesions (Figure 108-5B) usually have a shiny, waxy appearance surrounded by a violaceous, erythematos border. They may be warmer than the surrounding and contralateral skin. Rarely there may be local itching or tingling. The lesions are indurated, and they may be either superficial or can extend to muscle and bone. Occasionally with linear lesions, extensive fascial involvement may occur. Lesions heal with hyperpigmentation or hypopigmentation and generally soften with time. Atrophy of the subcutaneous tissues is common. Linear lesions, if untreated, may result in growth deformity, joint contracture, loss of muscle bulk, and marked extremity weakness.

Lesions on the face and head can take the form of either a “saber-cut”–like lesion (en coup de sabre) or progressive hemifacial atrophy (also known as Parry-Romberg syndrome), where the epidermal changes are minimal but there is marked dermal and subcutaneous atrophy (Figure 108-5C). These may coexist in the same patient. With time, as the unaffected side of the face grows normally, there is progression of the facial asymmetry even though the disease may be inactive. Facial lesions may be associated with hemiatrophy of the tongue (Figure 108-5D), dental abnormalities, and ocular abnormalities. A small number of children develop seizures.222

Pansclerotic morphea is rare but can be life threatening. There is marked thickening of the skin and deeper tissues involving the extremities and trunk, sparing the distal extremities. Although it is similar to systemic sclerosis in the extent of the fibrosis, internal organ involvement does not occur and Raynaud’s phenomenon is not common.

Extracutaneous signs and symptoms have been reported in up to 20% of patients.216 They are more common in patients with linear lesions. The most common is arthritis,
Hypergammaglobulinemia have been reported to correlate with active lesions, but this is not always the case. Rheumatoid factor is present in 10% to 25% and ANA positivity in approximately 50% of cases. Multiple specific autoantibodies have been reported, but antibodies to topoisomerase-I and centromere are distinctly unusual.221,225

**Treatment**

The treatment of localized scleroderma depends on the stage of the lesion, as well as the extent of involvement. Few controlled studies have been done; therefore treatment recommendations have relied on general experience. Plaque lesions can generally be treated topically with either corticosteroids and/or calcipotriene.226 Markedly indurated lesions may respond better to imiquimod.227 Topical tacrolimus may also be used. Systemic treatment is usually indicated for rapidly progressive lesions, for lesions crossing joint lines, and for lesions that are potentially cosmetically deforming. A combination of corticosteroids and MTX is generally recommended.228-231 Corticosteroids may be administered as monthly pulses or orally in a dose of 1 to 2 mg/kg with a taper over 3 to 6 months. MTX is not necessarily associated in the area of skin involvement. It is seen more commonly in patients with a positive rheumatoid factor. Neurologic manifestations of seizure and headache occur almost exclusively in patients with facial lesions. Ocular abnormalities including asymptomatic anterior uveitis were reported in 3% of one large series.223

**Diagnosis and Diagnostic Tests**

The diagnosis of LSc is usually made on the basis of characteristic cutaneous features. A skin biopsy can be of assistance when the diagnosis is not clear. Abnormalities consist of edema, an early infiltration by mononuclear cells, and excessive deposition of collagen. With time there is loss of skin appendages and rete pegs. Other skin diseases that may have a similar clinical presentation include lichen sclerosis et atrophicus, connective tissue nevus, collagenoma, and localized fibrotic disorders. The absence of significant internal organ involvement and Raynaud’s phenomenon help differentiate LSc from systemic sclerosis and other autoimmune conditions.

Laboratory investigations are nonspecific and show mild or no systemic inflammation (ESR, CRP). Eosinophilia and hypergammaglobulinemia have been reported to correlate with active lesions, but this is not always the case. Rheumatoid factor is present in 10% to 25% and ANA positivity in approximately 50% of cases. Multiple specific autoantibodies have been reported, but antibodies to topoisomerase-I and centromere are distinctly unusual.221,225

![Figure 108-5](image)
administered at a dose of up to 1 mg/kg or 15 mg/m² weekly. At higher doses, the subcutaneous route is probably more effective. Treatment should be administered for at least 2 years, and 1 year after all activity has disappeared because there is about a 30% chance of recurrence if treatment is stopped too early. MMF may be used for patients who have not responded to this combination. Imatinib, cyclosporine A, and tacrolimus have also been effective in a small number of cases. Ultraviolet A therapy is used more frequently in Europe with good success. Autologous stem cell transplantation may be required for patients with pansclerotic morphea.

Patients with facial lesions have undergone cosmetic repair with generally good outcomes. Surgery may also be required to lengthen Achilles tendons. In addition to medical and surgical treatment, a combined team approach is often required for patients with more extensive disease. Physical and occupational therapy are essential in improving and maintaining muscle strength, range of motion, and function. Psychosocial support is especially helpful for patients with facial lesions. Other medical personnel whose involvement may be required are neurologists, ophthalmologists, craniofacial surgeons, orthopedic surgeons, dentists, and orthodontists.

Disease Monitoring

To date, it has been difficult to monitor the course of the disease as clinicians have relied on insensitive measures such as warmth, color change, and change in size over time. Recently, some more objective measures have been studied including ultrasound, computerized skin score, and laser Doppler flow. A disease activity score has recently been developed and initial validation of a disease damage score has been undertaken. CARRA is currently establishing scores for activity and damage.

Outcome

Lesions tend to soften spontaneously over several years and to heal with pigmented change (usually hyperpigmentation) and subcutaneous atrophy. Linear limb lesions may lead to marked atrophy and joint contracture. Lesions may recur after many years of apparent inactivity. Neither self-esteem nor health-related quality of life appear to be diminished compared with controls, although not many patients with more disfiguring lesions were studied. Rarely patients have developed other autoimmune connective tissue disorders including systemic sclerosis and SLE. Patients with pediatric onset of LSc have a higher incidence of autoimmune disorders as adults.

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is included by some within the classification of localized scleroderma, and several authors have reported that children with EF have a disease evolution to morphea. EF is extremely rare in the pediatric population. Affected children present with marked induration of cutaneous and subcutaneous tissues of the upper or lower extremities and occasionally the trunk or face. Its onset may be preceded by intense exercise. Raynaud’s phenomenon, internal organ involvement, and nail-fold capillary abnormalities are rare but may occur.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) was initially reported as a disorder associated with a favorable prognosis and an excellent initial response to low-dose glucocorticoid therapy. It had a frequency of 0.3% in the U.S. Pediatric Rheumatology Database. Children present with arthritis, myositis, and cutaneous disease characteristic of scleroderma, SLE, or JDM. A decrease in aerobic capacity may occur from reduced muscle strength. Progression to a more scleroderma-like disease has occurred, with sclerodactyly and GI involvement, or an SLE-like disease may evolve. Nephritis may be more frequent and more severe in children than in adults. Children often have less pulmonary disease (hypertension) and more hematologic complications (thrombocytopenia) than adults. ANAs are present in high titers, often in a speckled pattern, to an extractable nuclear antigen and ribonuclear protein (RNP).

VASCUITIS

Vasculitis is a common clinical phenomenon in children. Vasculitis can occur in association with infections, medications, hypersensitivity reactions, and in the context of childhood systemic rheumatic diseases such as lupus. The most common primary or idiopathic vasculitis types are Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD). Incidences of vasculitis subtype vary widely depending on characteristics of populations such as ethnicity and the method of ascertainment.

Similar to adults, childhood vasculitis is categorized by predominantly affected vessel size as small, medium, or large vessel vasculitis. The histopathologic characteristics vary between diseases and include karyorhexis, neutrophilic infiltration and necrosis, giant cell formation, and lymphocyte infiltrates. In 2005 a classification system for childhood vasculitis was proposed. In 2008 the so-called “EULAR/PReS endorsed consensus criteria for childhood vasculitis” were validated.

Small Vessel Vasculitis

Inflammation of the small vessels is the most common vasculitis subtype in children. Typically exposure to infectious agents, medications, hypersensitivity such as serum sickness, or systemic illness can cause migration of neutrophils through the vessel wall, leukocytoclasis, and fibrinoid necroses. The resulting histologic diagnosis of leukocytoclasic vasculitis is a common result found on superficial punch biopsies done for suspected vasculitis. Additional immunofluorescence studies may reveal immunoglobulin (Ig) deposits along the vessel wall, evidence of immune complexes and/or complement activation. Deposition of IgA is the hallmark of HSP.

Henoch-Schönlein Purpura

HSP (or anaphylactoid purpura) is an IgA-mediated small vessel vasculitis predominantly affecting the skin and
causing a palpable purpura. Histologically, a leukocytoclastic vasculitis with extravasation of leukocytes and red cells, vessel wall damage, fibrinoid necrosis, and IgA1 deposition at the vessel wall and in the mesangium of the kidney can be found. Preceding upper respiratory tract infections are reported in more than 50% of children. A variety of bacterial and viral triggers, environmental stimuli, and host susceptibility factors such as autoinflammatory disease genes have been reported. HSP can occur before or during the course of systemic diseases such as antineutrophil cytoplasm antibody (ANCA) vasculitis or Crohn’s disease.

IgA appears to play a pivotal role in the pathogenesis of HSP. Abnormal glycosylation of the hinge region O-linked glycan of IgA1 has been implicated in the etiopathology of HSP: Abnormal IgA1 molecules were found to have a higher tendency to aggregate, interact with IgG, and form IgA-IgG complexes and deposits in the kidney. Similarly, serum levels of galactose-deficient IgA1 are elevated in Caucasian and Asian patients with IgA nephropathy. Schmitt demonstrated deposits of IgA-binding streptococcal M protein in the skin and kidney of HSP patients directly linking infection and vasculitis.

Table 108-8  European League Against Rheumatism/Pediatric Rheumatology European Society Endorsed Consensus Criteria for the Classification of Childhood Vasculitides

<table>
<thead>
<tr>
<th>Vasculitis Type</th>
<th>Classification Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominant Small Vessel Vasculitis</strong></td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Palpable purpura (mandatory criterion) plus at least one of: Diffuse abdominal pain, Any biopsy showing predominant IgA deposition, Arthritis or arthralgia (acute, any joint), Renal involvement (any hematuria and/or proteinuria)</td>
</tr>
<tr>
<td>Childhood granulomatosis with polyangiitis</td>
<td>At least 3 of the following 6 criteria must be present: Abnormal urinalysis (hematuria and/or significant proteinuria), Granulomatous inflammation on biopsy (if a kidney biopsy is done it characteristically shows pauci-immune necrotizing glomerulonephritis), Nasal sinus inflammation, Subglottic, tracheal, or endobronchial stenosis, Abnormal chest radiograph or computed tomography, Proteinase 3 ANCA or c-ANCA staining (sensitivity/specificity calculated for any positive ANCA)</td>
</tr>
<tr>
<td>Childhood microscopic polyangiitis</td>
<td>No proposed criteria; for description see text</td>
</tr>
<tr>
<td>Childhood Churg-Strauss syndrome</td>
<td>No proposed criteria; for description see text</td>
</tr>
<tr>
<td><strong>Predominant Medium Vessel Vasculitis</strong></td>
<td></td>
</tr>
<tr>
<td>Childhood (systemic) polyarteritis nodosa</td>
<td>Biopsy evidence of necrotizing vasculitis or angiographic abnormalities (mandatory criterion) plus at least one of: Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions, superficial or deep infarctions), Myalgia or muscle tenderness, Systolic/diastolic hypertension (&gt;95th percentile), Mononeuropathy or polyneuropathy, Renal involvement (proteinuria, hematuria, impaired renal function)</td>
</tr>
<tr>
<td>Childhood cutaneous polyarteritis nodosa</td>
<td>No proposed criteria; for description see text</td>
</tr>
<tr>
<td><strong>Predominant Large Vessel Vasculitis</strong></td>
<td></td>
</tr>
<tr>
<td>Childhood Takayasu’s arteritis</td>
<td>Angiography of the aorta or its main branches and pulmonary arteries showing aneurysms/dilatation, occlusion or thickened arterial wall not due to fibromuscular dysplasia (mandatory criterion) plus at least 1 of: Pulse deficit or claudication, Blood pressure discrepancy (&gt;10 mm Hg), Bruits, Hypertension, Acute-phase reactant (erythrocyte sedimentation rate &gt;20 mm/hr, C-reactive protein abnormal)</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasm antibody; c-ANCA, cytoplasmic antineutrophil cytoplasm antibody.
cases, arthritis/arthritis in 74%, abdominal symptoms in 51% including intussusception in 0.6%, renal disease in 54% including severe nephropathy in 7%, and acute renal failure in 2%. Scrotal edema was reported in 13%. Correspondingly, Dolezalova and colleagues described purpura present in 100% of Czech HSP patients; arthritis/arthritis in 52%; abdominal pain and/or GI bleeding in 40%; hematuria/proteinuria in 15%; and genital involvement in 2.8%. Eye findings including anterior uveitis can be seen in HSP patients.74

Skin disease in HSP has a characteristic appearance: Petechial or palpable purpuric lesions are located on dependent areas including lower legs and feet, buttocks, and arms. Lesions can have different sizes and stages ranging from fresh petechial rashes to confluent bruises. An associated edema is commonly found, hands and feet appear puffy, and scrotal edema may be present in boys. Children younger than 2 years have been reported to have more significant edema. Lesions occur in waves, and skin disease in HSP is reported to last from 4 to 8 weeks.272

HSP arthritis is often painful, nonerosive, and nonmigratory. Ankles, knees, hands, and wrists are most commonly inflamed. Arthralgias are found in a similar distribution. GI symptoms are common in HSP patients including intermittent abdominal discomfort, pain, and vomiting. Abdominal complications including intussusception are rare; however, they always have to be considered when a child presents with HSP features and complains of abdominal pain and possibly associated bloody stools. Oftentimes bowel wall thickening on ultrasound is detected.

Overall renal disease in HSP occurs in 40% to 50% of children and manifests itself as microscopic hematuria or low-grade proteinuria, which completely resolves in the vast majority.73 Older children may be at higher risk for nephritis.256 Overall progression to end-stage renal disease occurs in 1% to 3% of children.277 Renal biopsies are done in children with renal compromise and histologically demonstrate IgA nephropathy.275 The degree of damage on renal biopsy and the degree of proteinuria predicts poor outcome. Reported 10-year renal survival rates for children undergoing renal biopsies for HSP ranged from 73% to 90%.278 Though uncommon in HSP, overall IgA nephropathy and HSP nephritis represent the most common chronic glomerulonephritis in childhood.277

**Diagnosis and Diagnostic Tests.** Children with HSP may have a raised erythrocyte sedimentation rate (ESR) (57%), elevated serum IgA (37%), and proteinuria (42%).272 All children require serial urinalyses. Jauhola and colleagues demonstrated that HSP nephritis occurred on average 14 days after HSP diagnosis, and within 1 month in the majority of cases. The risk of developing HSP nephritis after 2 months was 2%. Laboratory tests or blood pressure measurement at onset did not predict the occurrence of nephritis. Overall specific diagnostic markers of HSP are not readily available. Alternative complement pathway markers including activated C3 and C4 were reported in children and adults and may be associated with disease progression.75 Urinary proteomic patterns and serum levels of galactose-deficient IgA1 are promising and are currently being studied.251

Skin biopsies are done to confirm the diagnosis of HSP and to exclude differential diagnoses. Overlapping clinical features may be found in infection, inflammation or medication associated leukocytoclastic vasculitis, rheumatic fever, poststreptococcal glomerulonephritis, lupus, and systemic vasculitis.252,253 Renal biopsies are performed in a select group of HSP patients.275

**Treatment.** In most children HSP is a benign disease and does not require specific therapy. There is significant variation demonstrated for inpatient therapy and evaluation of children with HSP, which may contribute to varying clinical outcomes.78 Immunosuppressive therapy of HSP targets severe disease presentations including nephritis and gastrointestinal vasculitis. In 2006, Ronkainen and colleagues published a randomized placebo-controlled trial demonstrating that prednisone reduces the severity of joint and abdominal pain, while having no effect on purpura, prevention of nephritis, or recurrence of HSP.255 A recent retrospective cohort study of 1895 children discharged with HSP between 2000 and 2007 from 36 tertiary care children’s hospitals in the United States determined that early corticosteroid treatment was associated with significantly less abdominal surgery, endoscopy, and abdominal imaging during hospitalization suggesting a protective effect of corticosteroid therapy for abdominal complications of HSP.256 In contrast, a prospective study from Finland reported that corticosteroids although alleviating clinical symptoms, did not alter the clinical course of HSP during 6 months of follow-up. Prednisone prophylaxis did not affect the timing of the appearance of nephritis.275 The addition of cyclophosphamide did not show a benefit in adults with HSP nephritis in a small trial.257 A stepwise approach is often used, including the use of nonsteroidal anti-inflammatory medication for mild HSP, corticosteroids for moderate to severe HSP, and addition of angiotensin-converting enzyme (ACE) inhibitors for nephritis. Evidence is emerging that treatment with high-dose IV pulse methylprednisolone coupled with azathioprine or cyclophosphamide may be beneficial in patients with severe nephritis.287 Cyclosporine also has been successfully used for severe nephritis.288

**Outcome.** In the majority of children HSP is a self-limiting disease, which resolves within 4 to 6 weeks.258 Patients with microscopic hematuria and trivial proteinuria have an excellent prognosis.260 In contrast, 30% of pediatric HSP patient with nephritis will have renal impairment and 5% will develop end-stage renal disease.291 Recurrence of HSP is seen in a third of patients; symptoms resolve within 4 to 6 weeks in the majority of patients. Children older than 8 years of age and those with nephritis are significantly more likely to experience recurrences.292

**Antineutrophil Cytoplasm Antibody Vasculitis**

The group of childhood systemic vasculitides associated with ANCA include granulomatosis with polyangiitis (GPA; formerly known as Wegener’s granulomatosis), microscopic polyangiitis (mPA), and Churg-Strauss syndrome (CSS). The conceptual framework provided by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis is commonly accepted for childhood ANCA vasculitis. Necrotizing small vessel vasculitis of venules, capillaries, arterioles, and small arteries is the hallmark of ANCA vasculitis. Pathogenetic studies were not primarily done in children and are therefore not
covered here. Pauci-immune necrotizing and crescentic glomerulonephritis, as well as hemorrhagic pulmonary capillaryitis, frequently present as pulmonary-renal syndrome. Limited phenotypes including pauci-immune glomerulonephritis with ANCA and nonrenal, upper respiratory tract, or limited GPA are commonly included in the group of ANCA vasculitides of children and adults. These diseases are rare in childhood. However, recent collaborative efforts such as “A Registry for Childhood Vasculitis (ARCHiVe)” have substantially increased the knowledge and understanding of childhood ANCA vasculitis.

**Definition and Classification**

Granulomatosis with Polyangiitis. The proposed EULAR/PReS-endorsed consensus criteria for GPA are shown in Table 108-8. The sensitivity as determined in the validation process described earlier was found to be 93.3%, and the specificity was 99.2%, when including evidence of any ANCA. Cabral and colleagues have recently validated the proposed criteria in a large multicenter cohort of children with systemic vasculitis (no HSP) and determined a diagnostic sensitivity of 73.6% and specificity of 73.2%.

Microscopic Polyangiitis. In children, MPA is a rare diagnosis. No formal classification criteria were proposed for MPA in children by the “EULAR conference expert group.” Instead, the existing Chapel Hill description was modified by formally adding ANCA.

Churg-Strauss Syndrome. CSS (allergic granulomatosis) is even less common than MPA in children. No pediatric classification criteria exist, and therefore adult ACR criteria are commonly applied. The pediatric literature is limited to case reports and small series. A recent literature review identified a total of 33 children with systemic vasculitis (no HSP) and determined a diagnostic sensitivity of 73.6% and specificity of 73.2%.

Clinical Presentation

The clinical presentation of ANCA vasculitis is widely overlapping. In children, GPA and MPA patients are commonly reported in combined series. In the largest single-center cohort of 25 children, the median duration of symptoms before establishing the diagnosis was 2 months. Children presented most frequently with constitutional symptoms (96%) and glomerulonephritis (88%) with renal failure in half. Recovery from renal failure was uncommon (1/11). Upper airway disease was present in 84% including one child with subglottic stenosis. Overall, 80% had pulmonary involvement at diagnosis, most commonly nodules (44%) and pulmonary hemorrhage (44%). Five children with pulmonary hemorrhage required ventilation, and four children had venous thrombotic events. The ARCHiVe group reported 117 pediatric patients including GPA (n = 76), microscopic polyangiitis (n = 17), ANCA-positive pauci-immune glomerulonephritis (n = 5), CSS (n = 2), and unclassified vasculitis (n = 17). In the 65 of 76 who met ACR criteria for GPA, the median interval from symptom onset to diagnosis was 2.7 months (range, 0 to 49 months). The most frequently presenting features by organ system were constitutional (89%); pulmonary (80%); ear, nose, and throat (80%); and renal (75%). Zwerina and co-workers suggested that children compared with adults with CSS had a predominance of cardiopulmonary disease manifestations, less peripheral nerve involvement, and higher mortality.

Diagnosis and Diagnostic Tests

Raised inflammatory markers including ESR and CRP, leukocytosis, and positive ANCA are commonly found at diagnosis of ANCA vasculitis. Akikusa and colleagues documented ANCA positivity in 22 of 25 children. Cabral and co-workers identified cytoplasmic ANCA (c-ANCA) positivity in 66% of pediatric GPA patients, 93% of whom were anti-PR3 positive on enzyme-linked immunosorbent assay. Accordingly, 22% were perinuclear ANCA (p-ANCA) positive, of which 21% had anti-PR3 and 57% anti-MPO specificity. Endothelial cell markers including von Willebrand factor antigen, antiendothelial cell antibodies, and circulating endothelial cells are potential biomarkers.

Epidemiology

Childhood ANCA vasculitis is a rare group of diseases. In Southern Alberta, Canada, the average annual incidence of GPA in children was estimated at 2.75 cases per million per year, with a steep increase over the past 5 years to 6.39 cases per million per year. A recent study from Japan reported the adult MPA incidence at 14.8 per million, whereas GPA was present in 2 per million adult patients. Within the group of ANCA vasculitis, MPA may be more common than GPA in adults, while it is definitely less common in children. However, Reinhold-Keller and associates suggested that the incidence of GPA of all age groups was two to three times greater than those of MPA and CSS. There was no regional difference in incidence rates found. Girls are consistently more commonly affected than boys; the male-to-female ratio is reported to be 1:3 to 4.

Treatment

The treatment of ANCA vasculitis in children is grounded in knowledge gained from studies in adults. No randomized trials or prospective observational studies are available in children. The recently reported EULAR recommendations for management of vasculitis synthesize the available evidence. Children commonly receive induction therapy with cyclophosphamide and high-dose corticosteroids for severe disease, followed by a combination maintenance regimen with either MTX or azathioprine plus low-dose corticosteroids. Children with limited disease may be
which encodes a regulator of T cell activation.\textsuperscript{327}

transduction caspase-3 gene polymorphisms of proinflammatory genes such as the signal differs between ethnic groups. This may be related to genetic process in a susceptible host.

Kawasaki disease (KD) is better classified as an inflammatory "syndrome." Infectious triggers and possibly other environmental factors lead to a stereotypical inflammatory process in a susceptible host.\textsuperscript{321} Host susceptibility clearly differs between ethnic groups. This may be related to genetic polymorphisms of proinflammatory genes such as the signal transduction caspase-3 gene CASP3 or the ITPKC gene, which encodes a regulator of T cell activation.\textsuperscript{325,326}

Genes involved in vascular remodeling such as matrix metalloproteinases may confer an increased risk of vessel damage and aneurysm formation.\textsuperscript{317}

**Definition and Classification.** The diagnosis of KD remains grounded in recognition of a clinical pattern: Children, in whom the diagnosis of typical KD is made, present with a minimum of 5 days of fever plus at least four of five criteria including oral changes of cracked lips/strawberry tongue (as seen in 94\%), bilateral nonpurulent conjunctivitis (92\%), rash (90\%), erythema and/or swelling of hands and/or feet (77\%), and cervical lymphadenopathy (64\%).\textsuperscript{328}

The diagnostic criteria for KD have been systematically studied in children with incomplete clinical features. In 2004, the American Heart Association (AHA) proposed an algorithm for diagnosing and treating suspected incomplete KD.\textsuperscript{329} Yellen and coworkers tested the performance in a retrospective multicenter series of 195 patients with KD and coronary artery aneurysms. The authors demonstrated that applying the AHA algorithm would have significantly increased the rate of IVIG treatment from 70\% (classic KD criteria) to 97\%\textsuperscript{330} and possibly prevented aneurysms. Similarly, Heuc lyn and colleagues recently demonstrated a significantly increased detection rate of KD—in particular incomplete KD with coronary lesion—when applying the AHA algorithm.\textsuperscript{331}

**Epidemiology.** KD primarily affects young children; 80\% of cases occur in children younger than 5 years of age.\textsuperscript{332} Boys are more commonly affected than girls; the male-to-female ratio is reported to be 1.4 to 1.9:1.\textsuperscript{333} Recurrence rates of KD are estimated at 3\%.\textsuperscript{334} Atypical KD is more common in children younger than 1 year or older than 9 years of age, accounting for one-third of KD diagnoses in these age groups.\textsuperscript{328}

Incidence rates clearly vary between ethnic groups. Asian children are at highest risk: In 2010, Park and colleagues recently reported an average annual incidence rate of KD in Korea of 113.1 per 100,000 in children younger than 5 years.\textsuperscript{335} In Japan, the annual incidence rate was even higher at 218.6 per 100,000 children younger than 5 years of age.\textsuperscript{332} Around the same time, in the rest of the world annual KD incidence rates were reported between 5 and 13 per 100,000 children younger than 5 years.\textsuperscript{328,335-338}

**Clinical Presentation.** Fever in KD patients is typically continuous. It is reported to be either absent or less prominent or consistent in children younger than 1 year of age and older than 9 years of age. Eye findings include bilateral nonpurulent conjunctivitis, which is particularly prominent with fever. Other inflammatory eye findings including asymptomatic uveitis have been reported. Rash of all types can be associated with KD. The rash is also more prominent with fever. Frequently it is confluent in the diaper area and axilla in the acute phase. Skin peeling classically starts on the fingertips in the subacute phase. Blisters are uncommon. Oral changes include dry, red, and cracked lips; prominent follicles of the tongue (strawberry tongue); and an oral anaphema. Aphthous ulcers can be present, primarily when associated with a triggering herpes-group virus infection. Cervical lymphadenopathy is frequently asymmetric. The criteria state they should be 1.5 cm or greater. Nodes can be tender, and a secondary lymphadenitis can occur, which may require additional therapy. Hands and feet frequently appear puffy and erythematous.
Neurologic symptoms are common in children with KD: The majority of toddlers are extremely irritable. Often children are withdrawn, lethargic, and clingy or complain of headaches, in particular with fever. Transient hearing loss can be present in a significant number of patients, most commonly sensorineural hearing loss (20 to 35 dB). It may be related to salicylate toxicity in some children. Persistent hearing loss is rare.339

Other organ manifestations include acute arthritis,340 hepatitis,341 gallbladder hydrops, intussusception, or pseudo-obstruction presenting as acute abdomen,342 dysuria with sterile pyuria, genital swelling, and muscle pain and weakness.

**Diagnosis and Diagnostic Tests.** Inflammatory markers are commonly raised in children with KD. ESR and CRP, leukocytosis, anemia, mildly raised liver function tests, and low albumin levels are expected in children with acute KD.343,344 Laboratory markers are included in the AHA algorithm329 and have been used to predict adverse outcome.345

Because infections are commonly found in children with KD, an infectious workup is mandatory to detect concurrent ongoing infections that may require additional therapy. Cardiac evaluation in KD patients includes a chest radiograph, electrocardiogram, and echocardiography. DeZorzi and associates defined body-surface area-adjusted standards (z scores) for coronary artery abnormalities on echocardiography.346 These scores have subsequently been used to establish a classification system for the entire spectrum of coronary artery abnormalities including aneurysms.347 Follow-up echocardiography is required at 2 weeks in children with evidence of coronary damage and at 6 weeks in all children because vascular disease commonly peaks at 2 to 4 weeks.348

A severe complication of KD is increasingly recognized: macrophage activation syndrome (MAS).349 Latino and co-workers reported 12 of 638 KD patients who developed clinical and laboratory features of MAS including hepatosplenomegaly, cytopenia in two or more cell lines, hyperferritinemia and elevated hepatic enzymes, hypertriglyceridemia and/or hypofibrinogenemia, increased p-dimers, and evidence of hemophagocytosis on biopsy (4/12). Early recognition of MAS and increased immunosuppression are crucial.

**Treatment.** The first-line treatment for children with KD is IVIG at a dose of 2 g/kg.350 In addition, high-dose acetylsalicylic acid (ASA) at 30 to 50 mg/kg or 80 to 100 mg/kg is frequently used as an antipyretic and anti-inflammatory drug while the child is febrile. However, a metaanalysis did not find sufficient evidence for ASA treatment in KD.351 Conceptually, there is strong support for the use of ASA in KD because IVIG and ASA were found to differentially modulate the expression of TNF and its downstream effects in the KD animal model.352 Importantly, low-dose ASA has an antithrombotic effect by inhibiting the production of thromboxane A2 and prostacyclin in platelets.

Recurrence of fever after a dose of IVIG is commonly treated with a repeat dose of IVIG.353 Children with refractory KD, defined as failure to respond to IVIG retreatment commonly receive corticosteroid therapy. A trial exploring the efficacy of early corticosteroids for primary KD therapy in addition to IVIG did not demonstrate a significant benefit.349 In nonresponders TNF inhibitors have been used.353,354 Son and co-workers reported that patients treated with infliximab had a faster resolution of fever and fewer days of hospitalization.355 Abciximab is a monoclonal antibody against glycoprotein (GP)IIb-IIIa on platelets. A small study of 18 children with KD and large coronary artery aneurysms suggested that abciximab treatment may be associated with improved vascular remodeling.356

Children with KD require cardiology follow-up at 6 weeks including clinical assessment and echocardiography. Commonly, low-dose ASA treatment is discontinued in all patients in whom the coronary artery lesions have resolved. Children with evidence of coronary disease at 6 weeks require long-term care. In many centers asymptomatic KD patients are reassessed at 12 months and then discharged.

**Outcome.** The 5-year survival of children with KD is excellent at greater than 99%.318 However, one in 20 children with KD will develop permanent damage to their coronary arteries.357,358 Children may develop vascular aneurysms and stenoses beyond the coronary arteries (Figure 108-6). Early interventions including stenting or coronary bypass operations may be required.359 Even asymptomatic children with KD and aneurysms are at high risk of myocardial lesions.360 The long-term impact of “transient” coronary artery dilatations/ectasia remains to be determined.361 KD may lead to endothelial dysfunction and premature atherosclerosis.362 The psychosocial impact of KD was recently explored: Parents of KD patients report significant distress and anxiety even years after the acute illness.363

**Polyarteritis Nodosa**

Polyarteritis nodosa (PAN) is a rare necrotizing vasculitis of medium-sized vessels.321,364 The focal/segmental, transmural necrosis can lead to aneurysm formation. Classically lesions heal and scar with a palpable fibrotic nodule (nodosa). The
classic or systemic form can affect medium-sized arteries in multiple organs and typically presents with clinical and laboratory features of severe systemic inflammation. In contrast, cutaneous PAN is limited to the medium-sized arteries of the skin. It is more common and is characterized by periodic exacerbations often associated with Streptococcus infection.\textsuperscript{321}

**Definition and Classification.** The proposed EULAR/PReS-endorsed consensus criteria for (systemic) childhood PAN are shown in Table 108-8.\textsuperscript{296} The group modified the adult ACR PAN criteria by making biopsy evidence of necrotizing vasculitis or angiographic abnormalities a mandatory criterion.

The sensitivity as determined in the validation process described earlier was 89.6%, and the specificity was 99.6%. The mandatory criterion of biopsy evidence had the highest sensitivity and specificity (>80%). Peripher alneuropathy was the least sensitive (26%), and renal involvement was the least specific (37%) criterion.\textsuperscript{296} The consensus conference did not propose criteria for cutaneous PAN but recognized the need for a separate category.\textsuperscript{325} The disease characteristics were described as presence of subcutaneous nodular, painful, nonpuritic lesions with or without livedo reticularis with no systemic involvement except for myalgia, arthralgia, and nonerosive arthritis; biopsy evidence of necrotizing, nongranulomatous vasculitis; negative tests for ANCA s; and an association with streptococcal infections.\textsuperscript{255}

**Epidemiology.** Systemic PAN is a rare disease. The overall incidence is estimated at 2 to 9 per million,\textsuperscript{367} and varies among ethnicities.\textsuperscript{321} In a recent 5-year survey of all childhood vasculitis at 15 Turkish centers, PAN accounted for only 6% of cases. An association of systemic PAN with familial Mediterranean fever (FMF) was suggested.\textsuperscript{366} Associations with hepatitis B and other viruses with childhood PAN have been reported.\textsuperscript{321}

In 2004 an international PAN survey of 22 pediatric centers identified 110 children, of whom 63 children (57%) had systemic PAN and only 33 (30%) had cutaneous PAN.\textsuperscript{364} However, in many centers the number of children with cutaneous PAN is significantly higher than with systemic PAN. The association of cutaneous PAN with medications and systemic inflammatory/autoimmune diseases has been reported.\textsuperscript{367,369}

**Clinical Presentation.** Systemic inflammation often presents as fevers, fatigue, and weight loss in children with systemic PAN.\textsuperscript{321} Decreased perfusion through medium-sized vessels can cause focal organ ischemia including severe abdominal pain,\textsuperscript{70} cardiac ischemia, muscle pain, skin infarction with gangrene, livedo reticularis, and renal hypertension. The severe focal vessel inflammation can present as cutaneous painful nodules often located on the calves or feet, focal muscle pain, peripheral or cranial neuropathy, and inflammatory CNS lesions among others.\textsuperscript{321,371} Necrotizing vascular inflammation in systemic PAN can lead to fragility of the medium-sized arterial vessel wall and significant hemorrhage.\textsuperscript{372} Renal disease in systemic PAN is classically renal hypertension due to segmental artery disease; however, small vessel involvement presenting as isolated proteinuria, nephritic or nephrotic syndrome, and renal failure are reported in a series of 26 children from Turkey.\textsuperscript{373} Cutaneous PAN is characterized by the presence of deep skin nodules predominantly on the lower legs, which are frequently found at different stages of development. Most commonly a violaceous color or pigmentation with retiform appearance persists for months (Figure 108-7A-C). Ulceration can be a complication. Pain, arthralgias/arthritis, malaise, and moderate fever are associated symptoms in children with cutaneous PAN.\textsuperscript{374}

**Diagnosis and Diagnostic Tests.** Inflammatory markers including ESR and CRP are commonly raised in children with active systemic and cutaneous PAN.\textsuperscript{321} Organ function parameter may be abnormal. Specific diagnostic markers for PAN are not available. Characteristic PAN skin biopsy features are identical to adult PAN (see Chapter 90). Characteristic angiography findings include aneurysms and stenoses of the medium-sized arteries.\textsuperscript{321}

**Treatment.** The treatment of childhood systemic PAN is based on adult studies and recommendations and is summarized in Chapter 90.\textsuperscript{313} Pediatric case reports and series supported the efficacy of corticosteroids, combination immunosuppression, and biologic therapies including TNF inhibitors and B cell depletion using rituximab.\textsuperscript{316,321,319,373} Addition of antiplatelet agents may be required. Children with cutaneous PAN are commonly treated with nonsteroidal anti-inflammatory medication or corticosteroids. Refractory patients require immunosuppressive combination therapy. Prophylactic antibiotics are considered in children with evidence of Streptococcus infections.\textsuperscript{325}

**Outcome.** The 1-year and 5-year survival rates of 26 Turkish children with systemic PAN was only 72.5% and 60%, respectively.\textsuperscript{313} This is significantly worse than outcomes described by Ribi and colleagues of adult PAN 1-year and 5-year survival rates at 99% and 92%, respectively.\textsuperscript{315} However, Phillip and Luqmani reported a 5-year survival rate of 75% to 80% in a recent systematic review.\textsuperscript{318} Relapses are common in adults with PAN; Pagnoux reported 5-year relapse-free survival rates of only 59%; 86 patients (25%) died during the study interval of almost 6 years. In contrast, cutaneous PAN appears to have a good prognosis. No prospective long-term data are available for childhood PAN.

**Large Vessel Vasculitis**

Takayasu’s arteritis (TA) is the most common childhood large vessel vasculitis.\textsuperscript{376} Histologically, TA is indistinguishable from giant cell arteritis (GCA) in adults. TA and GCA may represent a disease spectrum rather than different entities.\textsuperscript{377,378} Both diseases are characterized by giant cells, which represent multinucleated cells formed by fusion of monocytes/macrophages and in TA can be found in the wall of large vessels including the aorta and its major branches.

**Definition and Classification**

The proposed EULAR/PReS-endorsed consensus criteria for TA are shown in Table 108-8.\textsuperscript{296} Angiographic abnormalities are a mandatory criterion. In addition, at least one of five criteria including pulse deficit or claudication, blood pressure discrepancy of greater than 10 mm Hg, bruits, hypertension, or elevated acute-phase reactant has to be present. The sensitivity and specificity as determined in the
validation process described earlier were 100% and 99.9%, respectively.\textsuperscript{257}

**Epidemiology**

The incidence of adult TA was recently reported at 0.8 per million in the United Kingdom.\textsuperscript{319} It may vary between ethnicities with higher incidences in Asia,\textsuperscript{380,381} Africa,\textsuperscript{382} and Latin America.\textsuperscript{383} No population-based pediatric data are available; however, children may account for up to 30% of patients in some studies.\textsuperscript{384-386} Most commonly, childhood TA is diagnosed in adolescence. All series have a female predominance ranging from 14:1 to 1.4:1. Recent case series reported a total of 99 children with TA.\textsuperscript{382,387-389} Associations of Mycobacterium tuberculosis and TA have consistently been suggested.\textsuperscript{390}

**Clinical Presentation**

Children with TA often present with clinical signs of organ ischemia and systemic inflammation. Most commonly, headache or associated neurologic deficits such as strokes, seizures or syncope, chest or abdominal pain, claudication of extremities, fever, and weight loss are the presenting symptoms.\textsuperscript{387,388} Examination frequently reveals hypertension, absent pulses, and bruits.

**Diagnosis and Diagnostic Tests**

The diagnosis of TA is based on clinical pattern recognition and confirmation by angiography. Inflammatory markers including CRP and ESR have limited sensitivity for active TA;\textsuperscript{391} no disease-specific markers have been identified. Hoffman and Ahmed demonstrated that there is a poor correlation between serum markers and vascular histopathology in adult TA.\textsuperscript{392} Angiography is the cornerstone of diagnosing and monitoring TA (see Figure 108-8A,B). Inflammatory arterial wall disease presents as arterial wall thickening, vessel stenosis, occlusion, or rarely aneurysms.\textsuperscript{393} Different vascular imaging modalities are used in TA, each with distinct advantages and limitations.\textsuperscript{394,395} Conventional angiography provides information about blood flow, perfusion pattern, collateralization, and degree of vessel stenosis. It reliably identifies clots or low-flow vessel segments posing a risk for subsequent artery to artery embolisms. Magnetic resonance angiography (MRA) is noninvasive and provides information about the characteristics of the vessel wall including thickening, contrast enhancement, and surrounding soft tissue inflammation.\textsuperscript{396} CT angiography may provide similar information as MRA; however, the associated radiation exposure often limits its use in children. Recent studies highlighted the utility of 18F-fluorodeoxyglucose (18FDG) positron emission tomography scan.\textsuperscript{397} Doppler ultrasound correlates well with angiography in delineating homogenous wall thickening in the aorta and its branches. It may be a promising tool for childhood TA.\textsuperscript{398}

**Treatment**

Corticosteroids are the cornerstone of medical TA treatment in adults and children.\textsuperscript{314} Combination
immunosuppression with cyclophosphamide was found to be effective in controlling disease activity in childhood TA.\textsuperscript{388,389} MTX was suggested in adult TA studies. Refractory childhood TA has been successfully treated with biologic therapies, primarily TNF inhibitors.\textsuperscript{400}

Surgical treatment includes stenting, dilatation, and bypass surgery.\textsuperscript{388} Corresponding to adult TA recommendations, the best time for vascular intervention in children is in inactive disease.\textsuperscript{401} A close collaboration between all treating subspecialties is mandatory.

**Outcome**

The overall outcome of TA is poor. The 5-year survival rate was reported to be 70% to 93%.\textsuperscript{318} Maksimowicz-McKinnon and colleagues gave a guarded prognosis of 93% attaining remission but only 28% having sustained remission of at least 6 months’ duration after prednisone was tapered to less than 10 mg daily. Angioplasty and vascular surgery were initially successful. Restenosis occurred in 78% of angioplasty and 36% of bypass/reconstruction procedures. More than two-thirds of TA patients had difficulty performing routine daily activities, and one-fourth were unable to work.\textsuperscript{382} Jales-Neto and co-workers recently determined that patients with childhood-onset TA had a significantly lower frequency of disease remission compared with adult-onset TA (24% vs. 56%) and more aneurysms (41% vs. 11%).\textsuperscript{403}

**Central Nervous System Vasculitis**

Childhood CNS vasculitis is an increasingly recognized inflammatory brain disease.\textsuperscript{384} CNS vasculitis is classified as secondary, when it occurs in association with a systemic illness including infection, malignancy, or rheumatic disease such as a systemic vasculitis (Table 108-9). Childhood primary CNS vasculitis solely affects the vessels of the brain and spinal cord.

**Definition and Classification**

The diagnosis of childhood primary CNS vasculitis is based on the modified Calabrese criteria for primary angiitis of the CNS (PACNS), which mandate (1) a newly acquired focal or diffuse neurologic deficit or a psychiatric manifestation in a patient 18 years of age or younger and (2) angiography and/or brain biopsy evidence of CNS vasculitis in the absence of a systemic underlying condition known to cause or mimic CNS vasculitis.\textsuperscript{404,405} Childhood PACNS (cPACNS) is further subdivided into angiography-positive cPACNS and angiography-negative, small vessel cPACNS (SVcPACNS), with the latter being confirmed on elective brain biopsies.\textsuperscript{406,407}

**Epidemiology**

The incidence of childhood CNS vasculitis is unknown. New clinical phenotypes continue to be recognized: Angiography-positive CNS vasculitis was found to be the underlying process in a large subgroup of vascular strokes, a condition neurologists may diagnose as transient cerebral arteriopathy (TCA).\textsuperscript{406,407} Recently, new clinical phenotypes of cPACNS have been described including refractory seizure status, movement disorder, and optic neuritis.\textsuperscript{408,409} Children with cPACNS may be diagnosed as “atypical” demyelinating disease.

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*Figure 108-8* Angiographic progression of Takayasu arteritis in a 6-year-old girl. Gadolinium-enhanced, reconstructed magnetic resonance angiography (MRA) demonstrates a critical superior mesenteric artery stenosis at diagnosis of Takayasu arteritis in a 6-year-old girl (A). Nine months later the repeat MRA demonstrates significant progression despite high-dose immunosuppressive treatment (B).
Table 108-9  Classification of Childhood Primary and Secondary Central Nervous System (CNS) Vasculitis

<table>
<thead>
<tr>
<th>Childhood Primary CNS Vasculitis (cPACNS)</th>
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<tbody>
<tr>
<td>Angiography-positive, nonprogressive cPACNS (NPcPACNS)</td>
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<tr>
<td>Angiography-positive, progressive cPACNS (PcPACNS)</td>
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<tr>
<td>Angiography-negative, small vessel cPACNS (SvPACNS)</td>
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<th>Secondary CNS Vasculitides in Children</th>
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<tr>
<td>Infection or postinfectious</td>
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<td>Bacterial infection</td>
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<td>Mycobacterium tuberculosis</td>
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<td>Mycoplasma pneumoniae</td>
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<td>Streptococcus pneumoniae</td>
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<td>Treponema pallidum</td>
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<td>Spirochete infection</td>
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<td>Borrelia burgdorferi</td>
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<td>Viral infection</td>
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<td>Cytomegalovirus</td>
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<td>Enterovirus</td>
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<td>Epstein-Barr virus</td>
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<td>Hepatitis C virus</td>
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<td>Human immunodeficiency virus</td>
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<td>Influenza virus</td>
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<td>JC virus (progressive multifocal leukoencephalopathy)</td>
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<td>Parvovirus B19 virus</td>
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<td>Varicella zoster virus</td>
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<td>West Nile virus</td>
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<td>Fungal infection</td>
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<td>Actinomyces</td>
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<td>Aspergillus</td>
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<td>Candida albicans</td>
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<td>Rheumatic disease</td>
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<td>Collagen vascular diseases</td>
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<td>Behcet’s disease</td>
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<td>Juvenile dermatomyositis</td>
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<tr>
<td>Morphea (en coup de sabre)</td>
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<td>Sjögren syndrome</td>
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<td>Systemic lupus erythematosus</td>
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<td>Systemic vasculitides</td>
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<td>Kawasaki disease</td>
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<td>Henoch-Schönlein purpura</td>
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<td>Microscopic polyarteritis</td>
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<td>Granulomatosis with polyangiitis</td>
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<td>Inflammatory bowel disease</td>
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<td>Hemophagocytic</td>
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<td>Lymphohistiocytosis</td>
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<td>Mitochondrial diseases</td>
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<td>Drug-induced central nervous system vasculitis</td>
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<td>Hemoglobinopathies</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Radiation</td>
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</table>

Clinical Presentation

Children with cPACNS can present with any focal or diffuse neurologic deficits or psychiatric symptoms. Children with angiography-positive disease typically present with headaches and strokes including acute hemiparesis, facial droop, hemisensory deficits, fine motor deficits, or dysphasia. Additional seizures and severe cognitive dysfunction are more commonly seen in progressive cPACNS. 406

Children with angiography-negative small vessel cPACNS may present with systemic features including fever, malaise, and flu-like symptoms, associated with headache, neurocognitive dysfunction, behavior changes, or intractable seizures. Focal neurologic deficits, optic neuritis, and myelitis can be presenting features. Previously healthy children may have developed a rapid neurologic deterioration and present with an acute encephalitis or may have had subacute progression of symptoms such as worsening seizures or behavior changes over weeks to months. 404

Diagnosis and Diagnostic Tests

The suspected diagnosis of cPACNS mandates a thorough evaluation. Systemic illnesses and other inflammatory and noninflammatory brain diseases have to be considered. 404 A diagnostic algorithm was recently proposed (Figure 108-9).

Inflammatory markers can be elevated in children with cPACNS, most commonly in the small vessel subtype. Von Willebrand factor antigen appears to correlate with clinical disease activity. Cerebrospinal fluid (CSF) analysis frequently reveals a mild pleocytosis with predominantly lymphocytes and occasionally elevated CSF protein. Frequently the opening pressure is raised.

The absence of laboratory markers does not exclude cPACNS. In fact, children with angiography-positive, nonprogressive cPACNS frequently have normal inflammatory markers. In contrast, angiography-positive progressive cPACNS and small vessel cPACNS patients commonly present with laboratory signs of inflammation. Serial testing may be required. Oligoclonal banding is found in children with confirmed small vessel cPACNS. 409

MRI studies identify ischemic, diffusion-restricted lesions and inflammatory, fluid-attenuated inversion recovery (FLAIR)-positive parenchymal lesions. 410,411 MRA and conventional angiography characterize vascular stenoses 411,412 (Figure 108-10A,B). Gadolinium-enhanced MRA sequences can demonstrate vessel wall enhancement and thickening in more than 85% of adult and pediatric patients with active cPACNS. 413

Brain biopsies confirm the diagnosis of angiography-negative cPACNS 409 (Figure 108-11). In contrast to adults, biopsies are not required in children with angiography-positive disease because the diagnosis is not confounded by arteriosclerosis. Elective brain biopsies can be lesonal as determined by MRI or nonlesional in the nondominant hemisphere. 409 The diagnostic yield is greater than 90% in

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**Figure 108-9** Proposed diagnostic algorithm for children with suspected central nervous system vasculitis. CSF, cerebrospinal fluid; CRP, C-reactive protein; DWI, diffusion-weighted imaging; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuated inversion recovery; MR, magnetic resonance; MRI, magnetic resonance imaging; OP, opening pressure; vWF, von Willebrand factor.
children. Nondiagnostic biopsies are most commonly found when inadequate specimens are obtained.\textsuperscript{409}

The differential diagnosis of childhood CNS vasculitis includes nonvasculitic inflammatory brain diseases such as neuronal autoantibody-mediated disease and demyelinating diseases. Neuronal autoantibodies should be tested when clinically indicated. In addition, noninflammatory vasculopathies have to be considered.\textsuperscript{404}

**Treatment**

No randomized controlled trials are available for CNS vasculitis in adults and children. A recent prospective observational cohort study evaluated the efficacy and safety of a 24-month induction-maintenance protocol for small vessel cPACNS,\textsuperscript{414} demonstrating a full neurologic recovery in two-thirds of children. Case reports and series describe the efficacy of other immunosuppressive treatments for different types of cPACNS.\textsuperscript{415-417} In children with nonprogressive cPACNS, adjunctive corticosteroids may prevent recurrent ischemic events and improve neurologic outcome.

**Outcome**

There is limited information about the long-term outcome of children with CNS vasculitis. In angiography-positive cPACNS, two-thirds have a monophasic, nonprogressive course. These children often present with large ischemic lesions due to proximal large vessel stenosis and ischemia in the vascular territory. Although progression of inflammation and involvement of other vascular beds is limited in this group, the associated neurologic deficit often exceeds the other subtypes characterized by progression of inflammation. Inflammation is reversible when recognized and treated early, as recently demonstrated in the small vessel cPACNS study.\textsuperscript{414} Disease flares are seen in a significant number of patients. Prospective collaborative studies are ongoing to further characterize the long-term outcome of children with CNS vasculitis worldwide.

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