The Diagnosis and Management of Systemic Lupus Erythematosus in Childhood

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Systemic lupus erythematosus (SLE) is an autoimmune systemic disease which has been diagnosed with increasing frequency in children and adolescents. It is therefore important for pediatricians to recognize its symptoms, diagnose it promptly, and initiate appropriate treatment. Because of his previous relationship with the patient, the family physician may be better equipped to deal with the issues surrounding school attendance, as well as interaction with the peer group and other family members. In this article, the emphasis is placed on the importance of a highly individualized decision-making process based upon the careful consideration of parameters of disease activity and major organ involvement. Drug side effects as they impact on the growing child, as well as newly emerging causes of, mortality in the young adults surviving childhood SLE, will be discussed.

Systemic lupus erythematosus should be viewed as a syndrome rather than a single disease.

Arthritis, fever, rash, weight loss, and fatigue are the most common presenting signs of childhood SLE. Arthritis resembles juvenile chronic polyarthritis; however, deformities and limitation of motion are rarely encountered. The rash has the typical malar distribution in about 50% of the patients. Some children may only have an erythematous blush or palmar erythema. Others may present with crusted, scaling lesions that may be rather extensive. The rash is photosensitive in about 40% of pediatric patients; sun exposure has been cited as one of the precipitating factors in the development of SLE.

Alopecia is a frequent presenting complaint. Sometimes the hair just above the forehead breaks, leaving short ends sticking out at the hairline. Alopecia and Raynaud’s phenomenon have been eliminated from the revised criteria for SLE, as these are frequently present in other rheumatic diseases; however, a significant number of children with SLE may present with Raynaud’s phenomenon, which may precede the development of other manifestations of SLE by many years.

Involvement of the reticuloendothelial system is prominent in children; up to 70% of pediatric patients develop lymphadenopathy at some time during the course of the illness; splenomegaly has been noted in 25% to 30% of patients, and hepatomegaly is present in 25% to 40% of patients along with minor abnormalities of liver function.
### TABLE

#### THE 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td><strong>1. Malar rash</strong></td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
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<td><strong>2. Discoid rash</strong></td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
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<td><strong>3. Photosensitivity</strong></td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
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<td><strong>4. Oral ulcers</strong></td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
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<td><strong>5. Arthritis</strong></td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
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<td><strong>6. Serositis</strong></td>
<td>a) Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR&lt;br&gt;b) Pericarditis—documented by ECG or rub or evidence of pericardial effusion</td>
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<td><strong>7. Renal disorder</strong></td>
<td>a) Persistent proteinuria greater than 0.5 g per day or greater than 3+ if quantitation not performed OR&lt;br&gt;b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed</td>
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<td><strong>8. Neurologic disorder</strong></td>
<td>a) Seizures—in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance OR&lt;br&gt;b) Psychosis—in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance</td>
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<td><strong>9. Hematologic disorder</strong></td>
<td>a) Hemolytic anemia—with reticulocytosis OR&lt;br&gt;b) Leukopenia—less than 4,000/mm³ total on 2 or more occasions OR&lt;br&gt;c) Lymphopenia—less than 1,500/mm³ on 2 or more occasions OR&lt;br&gt;d) Thrombocytopenia—less than 100,000/mm³ in the absence of offending drugs</td>
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<td><strong>10. Immunologic disorder</strong></td>
<td>a) Positive LE cell preparation OR&lt;br&gt;b) Anti-DNA antibody to native DNA in abnormal titer OR&lt;br&gt;c) Anti-SM—presence of antibody to Sm nuclear antigen OR&lt;br&gt;d) False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluororesent treponemal antibody absorption test</td>
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<td><strong>11. Antinuclear antibody</strong></td>
<td>An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus syndrome”</td>
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*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.*

Gastrointestinal manifestations are common and difficult to manage. Painful, intercurrent abdominal crises occur frequently and have diverse causes. Serositis, lymphadenitis, and vasculitis account for these crises. In addition, sudden onset of acute abdominal pain in a patient already under treatment may represent septic peritonitis.

Renal involvement is said to occur in up to 90% of pediatric patients. Urine must be carefully examined for the presence of protein, blood, white cells, and cellular casts. Quantitation of proteinuria and creatinine clearance becomes an important tool for determining the extent of renal involvement. Indications for renal biopsy are discussed below.

Hypertension as a presenting manifestation of SLE is rare, but may develop later. While daily steroids often accentuate this untoward complication, vasculitis or diffuse glomerulonephritis must be considered the primary cause. If not adequately controlled, persistently elevated blood pressure is associated with deterioration in renal function leading ultimately to irreversible renal failure. Hypertensive encephalopathy, strokes, and premature atherosclerotic heart disease continued on page 600
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ease (ASHD) are more likely to occur if blood pressure is not adequately controlled. 4

Signs of central nervous system (CNS) involvement in children with SLE are difficult to assess; these may be organic and related to the illness, therapy, or infectious complications, or they may be functional or a psychiatric reaction to the illness. Anxiety and depression over disfigurement caused by either the disease or its treatment are common problems and present great challenges to the physician. Seizures are rare; 5 chorea, another unusual manifestation of CNS involvement, is encountered more frequently in children than in adults, and almost always occurs early in the course. 6

Pulmonary manifestations have been reported in up to 60% of pediatric patients; with improved survival from other manifestations, pulmonary complications, including hemorrhage and pneumonitis, have emerged as leading causes of mortality in children. 7

The heart is relatively spared from serious disease; however, cardiac abnormalities are not uncommon. Abnormal findings include nonspecific heart murmurs, chest pain, ECG, or chest x-ray changes as well as pericarditis. Premature development of atherosclerotic heart disease emerged as an important cause of mortality in survivors of SLE. 8 Steroid therapy probably plays a role in the development of ASHD. Coronary artery vasculitis may also be a contributing factor.

LABORATORY FINDINGS

Hematologic phenomena in children with SLE are encountered frequently and include leukopenia, lymphopenia, anemia, and thrombocytopenia (Table). Autoimmune phenomena must be present in order to establish the diagnosis of SLE; circulating antinuclear antibodies detected by immunofluorescence are seen in all patients. The pattern and titer may vary, depending on the presence in the serum of autoantibody reacting with a specific nuclear antigen. 9 The presence of antibody to double-stranded DNA can, in many children, serve as an important parameter of disease activity, especially when used in conjunction with the total hemolytic complement assay. Lowering of the complement level, indicating complement consumption, is the most sensitive measure of tissue deposition. 10 Rheumatoid factors have been documented in up to 25% to 30% of children with SLE, a frequency higher than the incidence of rheumatoid factor activity in children with chronic arthritis. 3 Prolonged partial thromboplastin time (PTT), as well as false-position serologic tests for syphilis, can be documented in some patients. Recent studies of circulating anticoagulants in young women with SLE have attempted to elucidate the apparent dichotomy between the occurrence of thrombophlebitis in these patients and the presence of the inhibitor of prothrombin conversion which in vitro prolongs clotting pathways. 11, 12

TREATMENT

The management plan for a child with SLE must be highly individualized and may involve more than one specialist. While the pediatric rheumatologist and the pediatrician may lead the team, there is often the need for a nephrologist, dermatologist, and others, depending upon the expression of the disease in the particular child. While the goal of therapy is to prevent organ failure, the risk of the treatment must be carefully assessed and the normal function of the child in his or her environment maintained.

Children with mild disease can be managed with salicylates alone. Aspirin or nonsteroidal anti-inflammatory agents have been used successfully to control fever and arthritis. Rash and minor constitutional symptoms will often respond to hydroxychloroquine at a dose of 7 mg/kg/day. To prevent worsening of the rash, and sometimes systemic disease, the use of sunscreens and avoidance of sun exposure should be emphasized. Low-dose, alternate-day steroid therapy may at times be used to overcome constitutional symptoms in patients who do not exhibit major organ involvement.

Unfortunately, most children with SLE do not have mild disease and present with active nephritis, serious disease, or "lupus crisis." For those children, prednisone, up to 2 mg/kg/day in three or four divided doses, is used in order to abolish the specific mechanisms responsible for life-threatening processes. In general, this approach should be initiated only for acute, life-threatening episodes and maintained for the briefest time possible, using available clinical and laboratory parameters. Usually, significant improvement occurs within 2 weeks, at which time the dose may be consolidated to once daily.

Once there is normalization of total hemolytic complement and disappearance of antibodies to double-stranded DNA, the dose may be adjusted to alternate mornings by doubling the daily regimen and adding another 15% to 20%. If this is not tolerated, a more gradual weaning process may be used. The dose is then tapered slowly to the minimum level required for control of symptoms and laboratory parameters. Although each child behaves differently, in general, steroid requirement continues for 2 to 3 years, a time punctuated by periodic exacerbations which may require a brief period of increased steroid dosage. Again, the briefest period should be allowed with prompt weaning upon signs of remission. During the post-acute period, administration of both hydroxychloroquine and nonsteroidal anti-inflammatory agents should be encouraged whenever possible.

If the disease cannot be adequately controlled with alternate-day steroid therapy, or normalization of serologic parameters cannot be accomplished with steroids alone, the use of azathioprine or cyclophosphamide is indicated. Prednisone can usually be weaned dramatically following introduction of cytotoxic drugs.
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CRISIS MANAGEMENT AND SPECIFIC RECOMMENDATIONS FOR MAJOR ORGAN INVOLVEMENT

There is no question that improved survival of children with SLE is due largely to appropriate management of desperate situations. Children who are comatose, hypertensive, actively hemorrhaging, or seizing require vigorous intervention such as intravenous pulse steroid, cyclophosphamide, and plasmapheresis. Specifically, management of pulmonary hemorrhage (a frequently fatal, early complication of childhood SLE) should include all of the above measures. This approach, although reported only anecdotally, appears to have promise. Intravenous boluses of cyclophosphamide have been used in patients with active nephritis, severe thrombocytopenia, myositis, and CNS disease with promising results by Steinberg and coworkers at the National Institutes of Health. Massive doses of methylprednisolone have also been used with reported success for similarly affected patients.

The kidney is the most frequently affected major organ in SLE and it is the presence of renal involvement which usually dictates the management. The need for renal biopsy must be assessed individually. Since there is a potential for histologic change, the value of knowing the particular morphologic findings is limited to the time of the biopsy. However, activity and chronicity as seen on the biopsy specimens seem to have great predictive value. The greater the amount of fibrosis and scarring, the higher the chronicity index and the less chance of reversal of the lesion. Conversely, the greater the amount of active inflammation without scarring, the higher the activity index and the better the prognosis. Therefore, patients with high activity indices should do well and need to be treated with the least toxic regimen which will abolish inflammation. Conversely, patients with high chronicity indices, destined for renal failure and dialysis or transplantation, may benefit from high-dose immunosuppressive therapy and may unnecessarily suffer unacceptable toxicity. It is those patients who fall in between the extremes who may be the best candidates for cytotoxic therapy.

DRUG SIDE EFFECTS

When faced with a child with SLE, the physician finds no easy alternatives. As the etiology of SLE remains obscure, specific treatment without major side effects is not available. Corticosteroids remain the mainstay of management. Unfortunately, the patient ends up trading disease manifestations for unpleasant and often serious complications of therapy. First, patients must be warned about the risk of sudden steroid withdrawal causing iatrogenic Addison's disease. Second, the management, directed at reversing specific autoimmune phenomena, abolishes the ability...
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to both manifest and fight infection. Third, the development of diabetes mellitus and hypertension calls for addition of more drugs. In addition, iatrogenic Cushing’s syndrome, weight gain, and acne are more difficult stigmata to deal with for the adolescent patients. The lack of growth while on daily steroids needs to be recognized, and long-term complications such as cataracts and aseptic necrosis of bone may develop regardless of the steroid regimen used.

Cytotoxic therapy, although not resulting in disfigurement, hypertension, or diabetes, further compromises the immune system. Cyclophosphamide may cause hemorrhagic cystitis and, if used during puberty, may lead to ovarian and testicular failure.¹⁸

Most importantly, the potential for the development of secondary hematologic malignancies exists for both azathioprine and cyclophosphamide. Nevertheless, these drugs may be life-saving in some cases.

CONCLUSION

Lupus remains a therapeutic challenge but, with optimal management, survival and quality of life may be greatly improved.

REFERENCES