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Systemic Lupus Erythematosus in Children and Adolescents

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Synopsis

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can involve any organ system with a wide range of disease manifestations, and can lead to significant morbidity and even mortality. This article reviews the epidemiology, common clinical features, complications of disease, and briefly discusses the available treatment options. In addition, important medical and psychosocial issues relevant to the pediatrician caring for children and adolescents with SLE are discussed.

Keywords

pediatric; childhood; SLE; clinical features; neuropsychiatric; nephritis; diagnosis; treatment; damage; complications

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can involve any organ system, and may lead to significant morbidity and even mortality. In this article we review the epidemiology, common clinical features, complications of disease, and briefly address available treatment options. Further, we discuss important medical and psychosocial issues relevant to the pediatrician caring for children and adolescents with SLE.

Epidemiology

Childhood-onset SLE (cSLE) is a rare disease with an incidence of 0.3-0.9 per 100.000 children-years and a prevalence of 3.3-8.8 per 100.000 children.[1] A higher frequency of cSLE is reported in Asians, African American, Hispanics and native Americans.[2,3] When compared to two more common childhood autoimmune diseases, Juvenile Idiopathic Arthritis (JIA) and type 1 Diabetes, cSLE is around 10 to 15 times less common in white children.[4,5] However, in Asian children, cSLE is reported to be equally as common as JIA.[6] Most studies report a median age of onset of cSLE between 11-12 years; the disease is quite

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rare under the age of 5 years. As in adult onset SLE, approximately 80% of patients with cSLE are female.[7,8]

Classification and Diagnosis of cSLE

SLE is called the great mimicker, as the disease shares characteristics with many other (autoimmune) diseases. Especially when the classic malar rash is absent, diagnosing SLE can be a challenge. However, the astute pediatrician who considers SLE when presented with an unusual constellation of symptoms can recognize important patterns of disease manifestations crucial for the diagnosis. Most patients who are diagnosed with cSLE fulfill 4 or more of the American College of Rheumatology classification criteria for SLE (Table 1).[9,10] The criteria were designed for use in research studies, and we caution that the diagnosis of SLE should not solely be based on fulfilling these criteria. Although not rigorously studied in cSLE, the criteria have a greater than 95% sensitivity and specificity for the diagnosis of cSLE.[11]

Clinical Features

The current review will not attempt to describe all possible clinical manifestations but instead we focus on specific features that may be crucial for immediate recognition. Table 2 summarizes the frequencies of the common manifestations of cSLE.[7,12-17] SLE can affect any organ system, and leads to glomerulonephritis and central nervous system involvement arguably more often in cSLE than in adults with SLE.

Constitutional Symptoms

Patients ultimately diagnosed with cSLE frequently recount nonspecific constitutional symptoms that include fever, fatigue, anorexia, weight loss, alopecia and arthralgias.[7,12] These and other symptoms of diffuse generalized inflammation including lymphadenopathy and hepatosplenomegaly occur both at onset and during disease flares.

Mucocutaneous

The hallmark of SLE is the malar, or butterfly rash. The rash is seen in 60 - 85% of children with SLE, is generally described as erythematous, raised, non-pruritic, and non-scarring. The rash often extends over the nasal bridge, affects the chin and ears, but spares the nasolabial folds (Figure 1). It is photosensitive in more than a third of patients, and exacerbation of the photosensitive rash frequently heralds the onset of a systemic flare. Therefore, sunscreen with a high sun protection factor, as well as hats and protective clothing are recommended year round for all individuals with SLE.

Discoid rash, unlike in adult-onset SLE, is a rare manifestation of cSLE, occurring in fewer than 10% of patients.[7] This scarring rash most frequently occurs on the forehead and scalp, and its scaly appearance may be mistaken as a tinea lesion.[18] Table 3 summarizes the spectrum of dermatologic involvement, illustrating the diverse range of skin manifestations. Children and adolescents with SLE can develop a rash of (almost) any morphology, location and distribution, often presenting a diagnostic challenge to the primary care physician. A skin biopsy for histology aids in making the correct diagnosis, although biopsies of facial skin should be avoided. Non-scarring hair loss is common, but not specific for SLE. The alopecia is most often noted as thinning of the temporal areas of the scalp, although rarely it is more global and severe enough to require systemic immunosuppressive therapy. Nevertheless, for the affected child or adolescent, even mild hair loss can be distressing.

Involvement of the oral and nasal mucosa ranges from oral and/or nasal hyperemia to painless oral ulcers of the hard palate (Figure 2) and shallow nasal septal ulcers, and rarely,

nasal septal perforation. Due to both the location and painless nature of these lesions, the practitioner may overlook these findings if the degree of suspicion for SLE is low.

Musculoskeletal

The range of musculoskeletal involvement includes features that occur as a consequence of active SLE, and those that are secondary to treatment and/or chronic illness. Manifestations include arthralgias and arthritis, avascular necrosis, bone fragility fractures and secondary pain amplification. Arthritis occurs in 80% of patients with cSLE, and although the typical description is that of a painful polyarthritis, in practice a significant proportion of children with SLE experience minimal pain. The arthritis is identical in many ways to JIA, with effusions and decreased range of motion of both small and large joints and significant morning stiffness, however; the arthritis is almost always non-erosive and non-deforming. Arthralgias also commonly occur, and can be secondary to a pain amplification syndrome that occurs during or following a disease flare with resultant poor sleep and daytime fatigue, decreased cardiovascular conditioning and generalized pain.

Avascular necrosis can occur in patients treated with corticosteroids, and may be idiosyncratic to the dose of medication, although occurs more frequently in patients with SLE than with other diseases that are similarly treated with corticosteroids. In addition, osteoporosis is frequent, related to corticosteroid use and associated with an increased fracture risk.

Renal disease

Renal involvement occurs in 50 to 75% of all cSLE patients, and more than 90% of those who will develop renal disease will do so within the first 2 years after diagnosis.[7] Initial manifestations of renal disease range from minimal proteinuria and microscopic hematuria to nephrotic-range proteinuria, urinary casts, severe hypertension, peripheral edema, and renal insufficiency or acute renal failure. SLE most commonly affects the glomerulus (i.e. “lupus nephritis”), and the renal interstitium is rarely involved. In a patient with acute renal failure, thrombotic thrombocytopenic purpura (TTP), a thrombotic microangiopathy should be considered. TTP is discussed further below. As the severity of the nephritis often does not correlate with the severity of the clinical signs and symptoms, a renal biopsy should be performed for any suspicion of glomerulonephritis, including persistent mild proteinuria. Histologic diagnosis using a standardized classification (Table 4) guides treatment and aids in determining overall prognosis.

The classification of glomerulonephritis in SLE ranges from Class I (minimal mesangial) to Class VI (advanced sclerosing lupus nephritis), and contain descriptions of the mesangial involvement, degree of renal involvement (focal versus diffuse), and degree of involvement of the affected glomeruli (segmental versus global). In general, Class I (minimal mesangial) and Class II (mesangial proliferative) nephritis are mild lesions, and often require little to no immunosuppressive treatment as their natural history is favorable. Class III (focal proliferative) and Class IV (diffuse proliferative) lesions are the most frequent and severe lesions, with more than 80% of cSLE biopsies done at Hospital for Sick Children demonstrating one of these lesions.[7] Patients with these proliferative lesions have the highest risk of end stage renal disease (ESRD), and thus are treated with aggressive immunosuppression in attempts to avert this outcome. In contrast, Class V (membranous lupus nephritis), when it occurs as the exclusive lesion, rarely leads to ESRD, therefore, it is generally not treated with the same degree of immunosuppression as Class III or IV. However, Class V lesions are frequently observed in conjunction with other lesions (usually Class III or IV), and in this case the presence of the proliferative lesion directs therapy. Any

patient with SLE should have regular measurements of blood pressure, serum creatinine, and urinalysis for proteinuria, hematuria and evidence of urinary casts.

With the use of an aggressive treatment regimen, the incidence of ESRD is lower than in past decades, but still remains between 10 – 20% by 10 years from diagnosis.[19,20] Patients who develop ESRD require dialysis and can undergo renal transplant when a donor organ is available providing their disease is stable at the time of transplant. While a recent study noted that a third of cSLE patients with ESRD received a transplant within 5 years, another 22% died in that same time period.[21] Moreover, there is a risk of recurrence of nephritis in the graft kidney.[22] Overall, renal disease remains a significant cause of morbidity and mortality, with the possibility of disease flares even after years of remission.

Neuropsychiatric Involvement

SLE can involve both the central and peripheral nervous systems, with 19 distinct neuropsychiatric lupus (NPSLE) syndromes described (Table 5).[23] Up to 65% of cSLE patients develop NPSLE at any time during the disease course, and up to 85% of these patients will develop NPSLE within the first 2 years from diagnosis.[13,24] As many of the syndromes are infrequent, only the commonest are briefly outlined here.

Headache—Symptoms ranging from mild intermittent tension-type headaches, to daily, debilitating severe headaches that require prescription pain medication occur in 50 – 95% of patients.[13,25] Headache on its own can be a manifestation of active SLE, an indication of increased intracranial pressure, or of intracranial pathology such as sinus vein thrombosis especially in patients with antiphospholipid antibodies.[26] The occurrence of a new severe headache is a red flag in a patient with SLE, and immediate evaluation is required.[27,28]

Mood disorder—Depressive affect may be a normal and appropriate reaction for an adolescent dealing with a chronic disease, and thus attribution of depression to SLE is often challenging, and requires input from psychiatry colleagues. Major depression is not as frequent, and occurs in fewer than 10 - 20% of patients.[28,29]

Cognitive dysfunction—Impairment of cognition may be manifested by declining school performance and subtle difficulties with working memory and concentration tasks. Cognitive dysfunction is diagnosed with traditional neuropsychological testing, and has been observed in more than a third of asymptomatic cSLE patients.[29-31]

Psychosis—Hallucinations, predominantly visual but also auditory, are experienced by more than 10% of all patients with cSLE. Visual distortions are also common, with children reporting that the clock or light is distorted, or that the words on the page are “popping out”. The psychosis differs from that of primary psychiatric disease in that SLE patients have preserved insight, however, evaluation by a psychiatrist is recommended to assist with the diagnosis. Psychosis is frequently concomitant with cognitive dysfunction and acute confusional state.[24] Although investigations including MRI are often normal, aggressive treatment is recommended and frequently leads to complete resolution of symptoms.[32,33]

Seizures—Seizures are rarely seen in cSLE as an isolated event, but instead are frequently observed concomitant with other NPSLE syndromes. When they do occur, seizures are more often generalized than focal. Seizures may also occur in patients with CNS infections, severe hypertension, and in patients who have a recently recognized complication known as posterior reversible encephalopathy syndrome (PRES).[34,35]

In contrast to central nervous system disease, peripheral nervous system involvement is rarely observed in cSLE. Any cSLE patient presenting with new neurologic symptoms warrants consideration for a full diagnostic work-up. This may include a lumbar puncture, magnetic resonance imaging (MRI) with MR angiography and venography, electroencephalogram (EEG), and psychiatry, psychology and neurology evaluations as appropriate. Prior to attribution to SLE, other etiologies, in particular infection in the immunocompromised host, inappropriate prescription or illicit drug use, and new onset primary psychiatric disease must be considered in this predominantly adolescent population. Furthermore, patients rarely present with isolated features of one syndrome, and instead one may think of NPSLE as a series of overlapping symptoms, with coexistent symptoms in most patients.[24] Treatment of NPSLE depends on the clinical presentation, with psychosis and acute confusional state requiring the most aggressive immunosuppressants, while other NPSLE syndromes require therapies directed at the observed manifestations.

Hematologic Features

Cytopenias are common in cSLE, with more than 50% of patients presenting a decrease in at least one cell line.[7,12] Mild leukopenia (white blood cell count 3,000 – 4 000/mm^3) is the most common hematologic manifestation, and is usually due to lymphopenia (<1500 cells/mm^3), and less frequently neutropenia. While persistent lymphopenia may be a feature of active disease, neutropenia is more frequently a result of treatment (e.g. during treatment with cyclophosphamide). Anemia can take any form – the anemia of chronic disease which is normocytic and normochromic, iron deficiency anemia, or a Coombs' positive hemolytic anemia. Additionally, co-existent hemoglobinopathies such as sickle cell anemia and thalassemia trait must be considered. The workup includes iron studies, haemoglobin electrophoresis depending on the patients' indices, and other markers of hemolysis (reticulocyte count, haptoglobin, lactate dehydrogenase (LDH)). Hemolytic anemia, occurring in 10 - 15%,[12] is rarely severe enough to require transfusion. The thrombocytopenia observed in cSLE patients spans the spectrum from mild (<150,000) to profound (<10,000). However, in the absence of excess bleeding and/or bruising, little treatment is required for patients with a stable platelet count ≥ 20,000. The risks of bleeding (intracranial, intraperitoneal) are similar in SLE-related thrombocytopenia as they are in immune thrombocytopenic purpura (ITP), thus treatment is generally reserved for symptomatic or severe thrombocytopenia, and for patients with a history of severe thrombocytopenia who demonstrate an acute drop (i.e. flare) of their platelet count. Children and adolescents with chronic ITP should be assessed for the presence of antinuclear antibodies as they are at high risk of developing SLE.[36]

Antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) are present in 40% of patients with cSLE and in general associated with hypercoagulability. However, fewer than half of these patients will manifest a thrombotic or thromboembolic event.[27] The most common events are deep venous thrombosis, cerebral vein thrombosis and pulmonary embolus. Arterial events including stroke are less frequent.[37]

Gastrointestinal Involvement

Abdominal pain and discomfort are frequent, although not well characterized manifestations of SLE. Abdominal vessel vasculitis, with or without bowel perforation is rare.[38] A sterile peritonitis occurs in fewer than 10% of patients, leading to abdominal pain and ascites, and is akin to pleuritis and pericarditis (i.e. "serositis"). Pancreatitis is another well documented although infrequent manifestation of disease.[39] More often, abdominal pain is an adverse effect of prescribed medications including corticosteroids and non-steroidal anti-inflammatory drugs. As there is an association between cSLE and celiac disease, patients with persistent abdominal pain, diarrhea and/or weight loss should have the appropriate

testing done.[40] Elevated liver enzyme tests occur in up to 25% of patients, and may be due to a medication side effect, active SLE, fatty infiltration, thrombosis or infection. Testing for anti-liver kidney microsomal (anti-LKM) and anti-smooth muscle antibodies should be considered as this may point to primary autoimmune hepatitis that would require appropriate treatment.[41]

Cardiopulmonary Features

Serositis, namely pericarditis and/or pleuritis occurs in up to 30% of cSLE patients.[7,12] Symptoms of pleuritis include shortness of breath and pleuritic chest pain, while pericarditis presents with tachycardia, precordial or retrosternal chest pain, and the inability to lie flat. Either pericarditis or pleuritis may present with or without associated fever. An inflammatory process, serositis is one of the few SLE manifestations that is associated with a significantly elevated c-reactive protein (CRP),[42] and this laboratory test may be a useful clue. Although large pericardial and pleural effusions are seen on chest x-ray or echocardiogram, a serositis flare can present with only pain, bloodwork indicative of disease activity and increased CRP in the face of minimal findings on radiographic investigations.

Other rarer cardiopulmonary manifestations of SLE include myocarditis, non-infective (Libman-Sacks) endocarditis, interstitial pneumonitis, pulmonary hemorrhage and pulmonary hypertension. These are frequently severe, and can be life-threatening complications requiring prompt and aggressive treatment.[43,44]

Vascular Manifestations

Although SLE is not generally thought of as an active “vasculitis”, inflammation and/or thrombosis of almost any vessel is possible. Cutaneous vasculitis may manifest as small, tender nodules of the digitis, or palpable purpura (leukocytoclastic vasculitis) of the lower extremities, while retinal vasculitis (“cotton-wool spots”) and a small vessel CNS vasculitis are rare but recognized. Although often clustered under the term “vasculitis”, neither livedo reticularis nor Raynaud’s phenomenon are due to inflammation within a vessel wall, but instead are a result of vasospasm that is common in SLE. Finally, thrombotic thrombocytopenic purpura (TTP) is an infrequent but life-threatening manifestation of SLE. TTP is a thrombotic microangiopathy that is diagnosed upon observation of the triad of acute renal failure, thrombocytopenia and CNS involvement, closely resembling atypical haemolytic uremic syndrome (HUS). Treatment involves plasmapheresis and significant immunosuppression with corticosteroids and a second line agent.

Laboratory Findings

In the presence of suggestive clinical signs and symptoms, laboratory testing can support and confirm the diagnosis of SLE. A hallmark of SLE is the production of multiple autoantibodies. The commonest autoantibody is the antinuclear antibody (ANA), present in more than 95% of cSLE patients. In the presence of an ANA, it is appropriate to examine for specific autoantibodies including double-stranded DNA (dsDNA) and the extractable nuclear antigens(ENAs), recognizing that particular autoantibodies correlate with certain disease features.[45] The test for ANA has high sensitivity (>95%), but its specificity for SLE is as low as 36%.[46] Moreover, up to 10% of ‘healthy’ children will demonstrate a positive ANA. In SLE, anti-dsDNA antibodies have high specificity. Anti-Smith antibodies (anti-Sm, not to be confused with anti-smooth muscle antibodies indicative of autoimmune hepatitis) have the greatest specificity but low sensitivity for SLE. Both anti-ds-DNA and anti-Sm antibodies are associated with renal involvement, and anti-Sm may be associated with more severe disease. Other autoantibodies observed in cSLE include anti-ribonuclear protein (anti-RNP), anti-Ro (also known as anti-SSA) and anti-La (or anti-SSB) antibodies. Offspring of females with anti-Ro antibodies are at risk for Neonatal Lupus Erythemathosus

(NLE). NLE can lead to congenital heart block in these neonates, therefore, any adolescent female with cSLE and anti-Ro antibodies should be informed of this risk prior to any pregnancy, and referred for fetal echocardiogram monitoring by the end of the first trimester.

Other supporting features for SLE include hypocomplementemia (particularly C3 and C4 which are readily testable), cytopenia of one or more cell line as discussed earlier, and elevated ESR in the face of a normal C-reactive protein (CRP). Interestingly, CRP is often normal or only minimally elevated during a SLE flare, except when the flare is of serositis, or in the presence of concurrent infection or macrophage activation syndrome (MAS, see below and see also Chapter XX). Elevated liver enzymes can indicate fatty liver (secondary to corticosteroids), an adverse drug reaction or active SLE. Less common causes in cSLE would include an intrahepatic thrombotic process, or elevated transaminases as a reflection of muscle inflammation. Routine hematology and biochemistry tests are used to monitor disease status for flare and remission, medication side effects, and the effects of chronic disease and inflammation. Urinalysis should be done regularly for proteinuria, hematuria, and to examine for casts, while urine protein to creatinine ratios (spot, or 24 hour collection) are required for monitoring response to treatment of lupus nephritis.

Is it SLE?

The differential diagnosis of SLE is broad, and includes infection, malignancy and other inflammatory disorders. The adolescent female who presents with a photosensitive malar rash, painless oral ulcer, polyarthritis, Raynaud's phenomenon and pleural effusions is not a diagnostic challenge. However, initial symptoms may be vague, and red flags for the paediatrician include an older child or adolescent with any combination of persistent fever, fatigue, anemia, leukopenia, thrombocytopenia, lymphadenopathy, malar or other rash, alopecia, Raynaud's, unexplained weight loss, arthralgia or arthritis, headaches and other neuropsychiatric symptoms, or unexplained microscopic hematuria or proteinuria. See Table 6 for some of the more common differential diagnoses to consider in a patient presenting with systemic features. In contrast, Table 7 reviews some of the possible presentations of SLE as isolated organ system involvement without generalized features.

Complications

In addition to severe disease flares and complications due to medications, two further categories warrant mention: Infection and macrophage activation syndrome (MAS).

Infection

SLE patients in general are immunocompromised due to immune dysfunction intrinsic to the disease itself and due to the frequent use of high dose corticosteroids and other immunosuppressive treatment. Secondary infection is an important and frequent cause of morbidity and infection should be included in the differential of any patient with a suspected SLE flare .[47,48] Infections are frequently bacterial (60-80%), and one clue to their presence is an associated high CRP. Most bacterial infections require intravenous antibiotic treatment as SLE patients are known to have impaired defenses against encapsulated bacteria including pneumococcus, meningococcus, hemophilus influenza type B and salmonella. The polysaccharide capsule protects against direct complement associated lysis and the necessary specific antipolysacharide IgG2 response to the capsule is inadequately produced by SLE patients. Viral infections are known to mimic disease flares with normal or mildly elevated CRP. Systemic cytomegalovirus (CMV) infections are recognized, and may be severe or even fatal in the immunocompromised cSLE patient. They may occur as either a primary infection, or more often as reactivation of a previous infection. Patients receiving

corticosteroids are particularly at risk of herpes zoster, regardless of prior primary varicella disease or varicella vaccination. Patients receiving treatment with potent agents such as cyclophosphamide are at risk for other opportunistic infections such as pneumocystis jiroveci or cryptococcus.

Routine killed and recombinant vaccinations are safe, and recommended at their usual administration time. Yearly influenza vaccination (killed injectable vaccine, not the live attenuated nasal mist vaccine) is strongly recommended.[49] Additional recommendations include meningococcal and pneumococcal vaccination due to the specific susceptibility of SLE patients to these pathogens, as discussed above. For those who have not had either varicella disease or prior vaccination, it is recommended to give this live attenuated vaccine four weeks prior to start of immunosuppression, if at all possible. At present, there is no recommendation for herpes zoster vaccination in immunosuppressed children, and all other live attenuated vaccines (including measles, mumps and rubella) are contraindicated in a cSLE patient receiving systemic immunosuppressive drugs.

Macrophage activation syndrome (MAS)

MAS is an increasingly recognized complication in children and adolescents not only with SLE, but with several other rheumatic and infectious diseases. Its pathophysiology is not well understood, but reflects uncontrolled immune activation with increasing numbers of phagocytosing histiocytic cells infiltrating organs like the liver, spleen, lymph nodes and brain. Presentation can resemble an acute disease flare – with fever and fatigue, but with some differences in bloodwork and physical findings. Significant cytopenias (any or all of the white blood cell, hemoglobin and platelet counts), with elevated CRP, liver enzymes, bilirubin, lactate dehydrogenase, extremely elevated ferritin, and unexpectedly low (low or “normal”-range) ESR, along with high serum fasting triglycerides, fibrinogen and D-dimer should prompt rapid treatment with high-dose corticosteroid treatment and often hospitalization for this potentially life-threatening complication.[50] Intravenous immunoglobulin (IVIG) may also be given as part of initial therapy, although second line immunosuppressives such as cyclosporine may be required if the initial treatment is insufficient. In any cSLE patient presenting with clinical signs of disease flare, MAS should be included in the differential diagnosis. Finding a normal ESR and high CRP may differentiate between MAS and flare, but all features must be considered and rapid evaluation is required.

Treatment

The care of a child or adolescent with SLE requires a multidisciplinary approach, and ideally involves rheumatology, a primary care physician, nephrology (for any patient with renal disease), adolescent medicine, psychiatry and psychology, nursing, social work, physical and occupational therapy. Pharmacologic treatment is often aggressive, but tailored to the severity and extent of disease manifestations. Although few drugs are actually approved by the Federal Drug Agency (FDA) for use in patients with cSLE (only aspirin and prednisone), the use of multiple immunosuppressants on an “off-label” basis is the reality. All drugs have potential side effects, so the balance of risk versus benefit is always at the forefront of a treatment regimen. The anti-malarials, hydroxychloroquine (plaquenil) and chloroquine (aralen), remain a staple for the treatment of mild symptoms particularly rash and arthritis, and for disease maintenance therapy.[51] Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed primarily for musculoskeletal symptoms, and may also be used for serositis. Oral and intravenous corticosteroids remain the backbone of most therapeutic regimens, and are most effective for rapid disease control. More than 90% of all cSLE patients will receive corticosteroids at some point in their disease course.[52] The dose and duration of corticosteroid depends on the active manifestation being treated.

Immunosuppressive agents used in cSLE are given primarily for either improved outcome of patients with glomerulonephritis and/or NPSLE, or as a steroid-sparing agent for other manifestations that are resistant to a corticosteroid taper (e.g. persistent cytopenia or serositis). Methotrexate is predominantly prescribed for persistent arthritis in the absence of other systemic features, while azathioprine (imuran) is also effective for arthritis as well as vasculitic rash, cytopenias or serositis. Mycophenolate mofetil (cellcept) is now frequently used for the induction of remission in lupus nephritis, and for the maintenance of other significant organ manifestations.[53] For patients with glomerulonephritis, the choice of immunosuppressant depends on the histologic classification, in addition to other patient factors including race/ethnicity (for example hispanic and african-american patients may respond better to mycophenolate mofetil compared to cyclophosphamide)[54], drug insurance coverage, and patient compliance with a treatment regimen. Concomitant control of hypertension, peripheral edema and proteinuria with fluid restriction, low salt diet, and anti-hypertensives are important for optimal outcome. Angiotensin converting enzyme (ACE) inhibitors are particularly effective for reducing proteinuria. Although prescribed by some physicians, there are no recommendations for the use of lipid lowering statins in cSLE.

Cyclophosphamide (cytoxan), an alkylating agent, is reserved for the most severe and life threatening symptoms because of its risk for toxicities including infertility, infection and long-term risk of cancer. It is prescribed for severe NPSLE syndromes (psychosis, acute confusional state) [55] and in some cases for renal disease and other manifestations resistant to initial therapies, or for the patient who is noncompliant with oral medications. Management of NPSLE manifestations may also require antidepressants, psychotropic drugs, antiepileptics and anticoagulation as appropriate.

Contraception may be an important consideration for adolescents with cSLE. While non-pharmacologic options should be discussed, estrogen-containing oral contraceptive pills, patches, intra-vaginal rings or dermal implants are acceptable for patients who do not have antiphospholipid antibodies. Progesterone-only containing pills, intramuscular medroxyprogesterone, or the levonorgestrel-releasing intrauterine device are effective alternatives which will not increase the risk of thrombotic events in individuals with these antibodies.

Newer therapies are showing promise for the next generation of SLE patients. Rituximab (rituxan), a monoclonal antibody that binds and kills active B cells is effective for the treatment of cytopenias, and rheumatologists also use this drug in combination with other immunosuppressants for other disease manifestations.[56-58] Belimumab (benlysta), an anti-B-lymphocyte stimulator antibody, was recently shown to be effective for treatment of mild to moderate symptoms in an adult SLE population.[59] Remarkably, belimumab is the first new drug that has been FDA approved for the treatment of SLE in the past 50 years; however, it has not yet been studied for use in cSLE. Studies are underway examining several other biologics that target specific cells and mediators of the immune system, and we anticipate that over the next several years there will be many more effective treatments for both adults and children with SLE.[60]

Adolescent Issues to Consider for Optimal Disease Management

SLE is a lifelong disease, characterized by periods of flare and remission. Since the typical cSLE patient is an adolescent female, addressing the usual challenges of adolescence becomes crucial to ensure that the adolescents are making informed and correct choices. As the onset of SLE occurs at an already challenging time in life, further stresses and co-morbidities of disease should be minimized. At this age, teens are trying to exert their independence, they are learning self-sufficiency skills, and are “practicing” adult-type

problem solving. They often transition to new junior, middle and high schools, where the ability to establish new peer relationships is often influenced by physical appearance. Normal peer pressures including smoking, drug and alcohol experimentation, dating and sexual relationships, along with authority challenges are complicated by chronic disease. The opportunity for part-time employment and some financial freedom is often thwarted by their disease. Add in a new serious and chronic disease, and many teens with cSLE have significant issues with school, peers and their family relationships. Disease manifestations including malar and discoid rash, alopecia, and arthritis that may be painful or lead to writing difficulties, along with the possibility of significant cognitive dysfunction can make the life of a teenager even more challenging. Side effects of treatments compound these issues as high dose systemic corticosteroids lead to weight gain, “moon facies”, striae, and acne, while other treatments may cause alopecia or carry a risk of infertility. Therefore, it is not surprising that many teens with SLE are noncompliant with their medications and medical care, and are reluctant to attend school. Moreover, the transition to “adult care” comes at 18 years in most centers, an age that frequently brings other significant transitions – to post-secondary education, a frequent move out of their family home – added stressors to independently manage medications, appointments and their chronic disease. A comprehensive interdisciplinary clinical team that includes adolescent medicine, psychiatry and social work in addition to rheumatology and nephrology is critical to addressing many of these issues. Furthermore, issues of seamless transition to adult care must be addressed.

Long-Term Outlook

Studies have shown that patients with SLE do not achieve long lasting drug free remission and many patients have persistently active disease requiring long term immunosuppressive treatment.[61,62] However, cSLE patients are younger at diagnosis and have a more severe disease course than adult-onset SLE, therefore, they are prone to develop significant damage due to the disease or its treatment at a relatively young age.[7,63] Non-white ethnicity, especially patients of African-American (or Afro-Caribbean) or Hispanic descent, is associated with a worse outcome.[2,64,65] These studies need to be interpreted with caution, as the numbers of patients are frequently low, and socioeconomic status, a potential confounder, is not always taken into account. Mortality rates have decreased significantly over the past two decades, with 10 and 15 year survival exceeding 85%. However, with a median age of disease onset around 12 years, this means that at the age of 22 to 27 years up to 15% of cSLE patients have died.[66] Mortality in the first several years of disease is most commonly secondary to infection, ESRD or severe lupus flare, while cardiovascular disease plays a significant role in late mortality.

With longer survival there has been an increase in long term co-morbidities including premature atherosclerosis, and a 50-fold increased risk of myocardial infarction in young women with cSLE in their 30s and 40s.[67,68] Other long term complications include ESRD requiring dialysis and/or renal transplant and its concomitant morbidities, osteoporosis leading to increased bone fragility and fracture risk, hip (or other joint) replacement secondary to avascular necrosis, multiple hospitalizations due to infection and other treatment related complications. Moreover, SLE leads to an increased risk of malignancy, particularly lymphoma.[69]

Considering the above, it is not surprising that SLE interferes with many aspects of daily life. Adult-onset SLE has been associated with suboptimal mental and physical functioning and loss of work productivity.[70] Similarly, more than a third of cSLE patients report that the disease has negatively interfered with their education. Most adults with cSLE live on relatively low incomes with 11-23% living on full-time disability support.[71,72] Assessment

of health-related quality of life demonstrates significantly lower scores in cSLE patients compared to healthy controls, especially in the physical domain.[72-74]

Conclusion

Childhood-onset SLE is a lifelong autoimmune disease that may be difficult to diagnose due to its multisystem involvement, and heterogeneity of clinical manifestations. It follows a more aggressive disease course than adult-onset SLE, with greater disease activity at presentation and over time, and consequently leads to greater morbidity and mortality than adult-onset SLE. Moreover children with SLE have to deal with this unpredictable, relapsing-remitting disease during puberty, an already challenging time of life when physical appearance is important, self-esteem and identity are yet to be developed, and overestimation of personal skills regarding decision making and responsibility for their disease are frequent. Recognition of these cSLE specific issues is key to optimal disease management of children with SLE. Long term outcome studies of cSLE are limited, but new studies are underway to examine population based cSLE cohorts that have reached adulthood. The results from these studies will better determine the long-term outcome of cSLE and may form the basis of a more tailored management and treatment approach for children and adolescents with cSLE.

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