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Systemic lupus erythematosus and related disorders of childhood  
[Pediatric And Heritable Disorders]

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## Outline

Abstract

Current concepts of etiology and pathogenesis

Clinical manifestations

Central nervous system involvement

Pulmonary involvement

Osteoporosis in childhood systemic lupus erythematosus

Management

Antiphospholipid antibody syndrome

Neonatal lupus

Drug-induced lupus

Conclusions

References and recommended reading

Section Description

## Abstract

Systemic lupus erythematosus (SLE) remains a challenging autoimmune disease in term of its etiology, pathogenesis, and management. Much progress has been made in the past year in searching for the SLE susceptibility genes, particularly by several genome-wide screening groups. Cumulative evidence about the association of infections and hormones with SLE has been gathered. Researchers believe that childhood SLE involves more severe organ involvement than adult SLE. Central nervous system complicated lupus continues to be problematic because functional imaging can be abnormal in otherwise asymptomatic lupus individuals. Whether these abnormalities result from subclinical central nervous system involvement

or from false positives remains to be determined. With the wide use of corticosteroids as a cornerstone therapy for major organ involvement in childhood SLE, potential complications, especially those involving the growing bone or osteoporosis, are a cause of concern. Evidence suggests that regular exercise, as well as calcium and vitamin D supplementation, may help alleviate bone complications. Researchers have also updated information about pediatric antiphospholipid antibody syndrome. Follow-up studies on neonatal lupus and its pathogenesis have progressed, leading to a better understanding of its natural history and, in turn, to proper counseling of mothers of infants with neonatal lupus and of women with positive anti-Ro or anti-La antibodies. Drug-induced lupus in children is not uncommon. Minocycline and zafirlukast have been increasingly used, and were reported to induce lupus in children.

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Abbreviations:ACAs anticardiolipin antibodies, ANCA antineutrophil cytoplasmic antibodies, anti-N antineuronal cell antibody, anti-P antiribosomal-P antibody, APTT activated partial thromboplastin time, APAs antiphospholipid antibodies, BMD bone mineral density, CHB congenital heart block, CNS central nervous system, DIL drug-induced lupus, EBNA Epstein-Barr nuclear antigen, EBV Epstein-Barr virus, ELISA enzyme-linked immunosorbent assay, LACs lupus anticoagulants, NLE neonatal lupus, PARP poly ADP-ribose polymerase, PFT pulmonary function testing, SLE systemic lupus erythematosus, SLEDAI SLE Disease Activity Index, SPECT single photon emission computed tomography,

Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease characterized by the production of numerous autoantibodies. Organ injury is secondary to either direct binding of autoantibodies to self-antigens or to deposition of immune-complexes in vessels or tissues. It is estimated that 15-17% of lupus patients present before the age of 16 [1]. It has been estimated that 5,000-10,000 children are affected by SLE in the US (corresponding to an estimated prevalence of 5-10 children with SLE per 100,000 population) [2]. Childhood SLE has been reported to have more severe organ involvement, but this conclusion may be the result of selection bias [3,4].

Current concepts of etiology and pathogenesis

Systemic lupus erythematosus results from the interaction of genetic susceptibility and environmental factors. Familial clustering and the increased concordance rate in monozygotic twins (24-57%) compared to dizygotic twins and siblings (2-5%) demonstrate the important role of genetic susceptibility. Early complement component genes, as well as HLA class II and III, Fc[gamma]RIIIa, Fc[gamma]RIIIa, mannose-binding protein, SSA/Lo, CR1, IL-6, IL-10, Bcl-2, Ig Gm and Km allotypes, T cell receptor and HSP-70 have all been associated with SLE or lupus nephritis in case-control studies [5,6\*,7\*]. Mehrian et al.[8], studying the association of the apoptosis regulating genes Bcl-2, IL-10, Fas-L, and CTLA-4 in a large Mexican-American cohort, demonstrated that Bcl-2, IL-10, and Fas-L associate with SLE, but that the CTLA-4 gene does not. These researchers were also able to demonstrate a synergistic effect between the susceptibility allele 193 of the Bcl-2 gene and the susceptibility allele 127 of the IL-10 gene in this ethnic group. Three additional reports regarding SLE susceptibility genes were published recently. Moser et al.[9\*\*] scanned the genome in 31 black and 55 white multiplex pedigrees, and demonstrated genetic linkage at 1q23, 1q31, 13q32 and 20q13 in both ethnicities; 1q41 and 11q14-23 in African-Americans. Using multipoint nonparametric methods, Gaffney et al. found the best linkage to be near the HLA locus (6p11-p21) and three other loci with

lod score > 2: 16q13, 14q21-23 and 20p12 in 105 SLE sib-pair families [10\*\*]. Finally, Shai et al.[11\*\*] studied SLE multiplex families, mainly Mexican-American

(43) and white (37) families, by genome-wide search using nonparametric linkage analysis. They could not demonstrate the major susceptibility genes segregating in these families as shown by other groups. However, the strongest evidence for linkage was identified at locus 1q44, mainly from the Mexican-American subgroup. Other peak linkages included loci 1q23-24, 1p21, and 18q21-22 (contains Bcl-2 genes), which were detected in both ethnic groups. Interestingly, loci 1q23-31, which contain Fc[gamma]RII, have been detected by Moser et al.[9\*\*] and Shai et al.[11] for the potential linkage in their population. The loci 1q41-44 have now been identified in four independent evaluations of the SLE genome [6\*, 9\*\*, 10\*\*, 12]. Furthermore, Tsao et al.[13] have recently narrowed loci 1q41-42 from 15 cM to 5 cM in an extended sample and have tested three candidate genes (PARP, TGFB2, and HLX1) for association with SLE. From the family-based transmission-disequilibrium

test, PARP (poly ADP-ribose polymerase) is the only gene associated with SLE in this particular cohort. The function of PARP is unclear, but evidence from animal models suggests that it may be involved in DNA repair and apoptosis induction [13]. The differences in the strength of the strongest linkages found by these groups underscore the importance of racial factors and the complexity of the genetics of SLE. These susceptibility loci still must be confirmed by testing in a large multi-ethnic group.

Many case reports and animal experiments suggest that infectious agents and other environmental factors have a causal role in the development of SLE [14\*,15]. Autoantibodies against the spliceosome (anti-Sm) are quite specific for SLE. The peptide PPPGMRPP, derived from the amino acid sequence of Sm B/B', appears to share homology to the peptide PPPGRRP from the Epstein-Barr nuclear antigen-1 (EBNA-1) [16]. This finding prompted investigators to further study the association between the Epstein-Barr virus (EBV) and SLE. In a study of 117 children and young adults from two cohorts, seroconversion against EBV virus was present in 99% of SLE patients compared to 72.1% and 72.2% in disease control groups (juvenile rheumatoid arthritis and childhood myositis, respectively), and 70% in 153 normal age-matched controls. Seroconversion against cytomegalovirus and varicella zoster virus were not different from the control groups. Investigators studying a group of adult lupus patients recently found that 50% of a group of lupus patients, and all of the acute infectious mononucleosis patients studied, produced IgG antibodies against EBNA-2 derived synthetic peptide, which has been shown to have high homology to SmD1 ribonucleoprotein [17]. None of the EBV seropositive normal controls produced these antibodies. This strong association could result from the intrinsic susceptibility of lupus patients to EBV infection or EBV-infected individuals may be prone to developing lupus. These hypotheses must be investigated further. Molecular mimicry between the peptides from spliceosome and EBNA and epitope spreading are possible mechanisms for this association. Further studies are required to determine the EBNA seroconversion rate in a larger population. Cytomegalovirus, varicella zoster virus, and other endogenous/exogenous retroviruses have also been reported to occur with increased frequency in patients with SLE [14,18].

Recent observations from the Netherlands have suggested that females who develop lupus during their reproductive years (ages 17-47) have 4.2 times greater relative mortality risk during the course of the disease than individuals with disease onset during ages when female sex hormone levels are normally lower. Although this data must be confirmed in a larger scale study, the relationship of sex hormones and SLE has been long recognized [19]. The effect of 17[beta]-estradiol

(E2) on the immune system has been well described. Kanda et al. showed that E2 in vitro polyclonally enhances IgG and anti-dsDNA production by B cells from SLE patients [20]. E2 has also been shown to increase IL-10, but not IL-1, IL-2, IL-4, IL-6 production by peripheral blood monocytes from SLE patients. IL-10 acted additively with E2 in increasing B cell antibody production, suggesting that E2 may increase polyclonal IgG production. E2 may also increase anti-dsDNA production by active SLE-B cells by promoting monocyte IL-10 production. An additional role for estrogens in the pathogenesis of SLE is suggested by the demonstration by Rider et al. that estradiol increases calcineurin expression in cultured T cell from patients with lupus [21]. Calcineurin may in turn alter cytokine gene regulation and eventually T-B cell collaboration. In contrast, testosterone has been shown to decrease IgG production by SLE patients' peripheral blood mononuclear cells in vitro. These findings suggest that imbalance of the sex hormone ratios may contribute to the immune dysregulation in patients with lupus [20]. Other environmental insults in association with the development of SLE were elegantly and recently reviewed by Cooper et al. [14\*].

Impaired immune complex clearance secondary to either complement receptor defects (CR1, CR2) or Fc[gamma] receptor (Fc[gamma]RII, Fc[gamma]RIII) malfunction plays an important role in tissue injuries [22]. Apoptotic blebs and bodies, which contain nucleosomal DNA, Ro, La and small nuclear RNP, are thought to induce autoreactive immune responses by serving as a source of autoantigens. Herrmann et al. [22] have demonstrated defective apoptotic cell material engulfment and clearance in monocyte-derived macrophages from lupus patients. This may impact on immunopathogenesis of lupus in several ways. First, the persistence of circulating autoantigens may result in immune complexes, which induce tissue injury. Second, materials may directly deposit on the glomerular basement membrane, causing in situ immune complex formation and triggering inflammation. Third, these materials can be presented to T cells by other antigen-presenting cells, thereby propagating an autoimmune response [22].

Regarding other autoantibodies that are a hallmark of SLE, recent evidence of the importance of antiribosomal-P antibody (anti-P) in children was noted by two groups. Anti-P has been reported in association with aggressive SLE, hepatitis, nephritis, and psychosis [23]. A higher prevalence of anti-P in juvenile SLE from three cohorts compared with the prevalence of anti-P in adults (41-63% vs 7.7%) was shown by Reichlin et al. [24\*\*], using both enzyme-linked immunosorbent assays (ELISA) and western blot assays. Changes in anti-P titer also paralleled the changes in anti-dsDNA and strongly correlated with the disease activity as measured by SLE Disease Activity Index (SLEDAI) scores in these studies. In addition, the presence of both anti-P and anti-dsDNA strongly associated with nephritis in this cohort, suggesting a potential role for anti-P in the pathogenesis of lupus nephritis. This may explain the differences in prevalence of anti-P found in various studies; the level of anti-P may fluctuate with disease activity. Interestingly, anti-P can be detected in both healthy adults and children as early as 8 months of age. Normally these antibodies are masked by IgG antibodies, which are believed to be anti-idiotypic antibodies. Primary anti-P are IgG isotype although children

Antineutrophil cytoplasmic antibodies (ANCA) also require mention. ANCA have been recognized as an aid to diagnosis in certain forms of systemic vasculitis and may be a marker of the disease activity [25\*]. ANCA are also described in individuals with a variety of autoimmune diseases, including SLE. In a large European cohort of 566 SLE patients (age 13-79) drawn from seven European countries, the prevalence of ANCA was 16.4% using the indirect immunofluorescence assay [26]. The majority were p-ANCA. The associated clinical findings included

serositis, livedo reticularis, venous thrombosis, and arthritis. In a recent report [27], ANCA was positive by indirect immunofluorescence assay in 16 of 21 childhood SLE patients (76.1%), without any correlation between ANCA positivity and disease activity or organ involvement. Positivity to ANCA from SLE serum may be the result of polyclonal B cell activation and crossreactive antibody production and be only an epiphenomenon.

## Clinical manifestations

### Central nervous system involvement

Central nervous system (CNS) lupus remains difficult both to manage and to investigate since the brain is not easily accessible. Assessment of CNS lupus is further complicated by a wide spectrum of symptoms, ranging from mild headache or cognitive deficit to overt psychosis and coma. Unusual manifestations, including pseudotumor cerebri and leukoencephalopathy, have also been described [28]. CNS involvement in children with SLE is found in 20-30% of patients (depending on the definition used) with mild involvement in up to 45% of children compared to 30-70% reported in adults [2]. Serum Anti-P and cerebrospinal

fluid antineuronal cell antibody (anti-N) levels are elevated in lupus psychosis patients, and elevated anti-N levels appear to correlate with disease activity, as shown by Isshi and Hirohata [29]. High CSF anti-N levels were also found in lupus patients with organic brain syndrome and other patients with non-psychotic CNS lupus. These findings suggest both anti-P and anti-N may play an important role in the development of CNS lupus.

The diagnosis of CNS lupus is complicated by the lack of uniformly accepted diagnostic criteria and the absence of sensitive and specific diagnostic laboratory tests [30-32]. The absence of uniform criteria makes it difficult to compare studies. The confounding effects of corticosteroid therapy, reactive psychiatric disease, and/or adjustment disorders that commonly occur in sick children must also be considered. Several studies have shown that functional imaging studies, including single photon emission computed tomography (SPECT) and positron emission tomography scan, are more sensitive than structural imaging studies (computed tomography and magnetic resonance imaging) in detecting CNS abnormalities in lupus, but SPECT, in particular, has very poor specificity [30-37]. SPECT measurement of changes in regional CNS blood flow was more sensitive than measurement of changes in glucose metabolism by positron emission tomography scan [34]. However, no correlation was found between clinical symptoms and the extent or site of functional alteration by SPECT. Using this imaging study to follow the clinical course of CNS lupus remains controversial [31,32,36,37]. The transient nature of neuropsychiatric manifestations

may also affect the sensitivity of such functional studies. Nonneuropsychiatric lupus patients have abnormal SPECT studies in 13-70% of cases as demonstrated by several investigators [30,31,33]. Although some argue these cases may represent subclinical CNS involvement, one cannot exclude the possibility of false positive results. Large-scale studies with longer follow-up may address the evolution from asymptomatic to symptomatic neuropsychiatric manifestations in these patients. Although magnetic resonance imaging fails to detect CNS abnormalities in as many as 27-60% of cases, it may be more sensitive than positron emission tomography or SPECT for the detection of white matter lesions [30,32]. Interestingly, multiple small high intensity white matter lesions found in CNS magnetic resonance imaging from SLE patients did not correlate with specific neurologic features, the use of corticosteroids or other immunosuppressive

agents, or immunologic disease markers [33]. Recently, Petropoulos et al.[38], using automated T2 quantitative magnetic resonance imaging, reported a marked increase in gray matter T2 signal in major neuropsychiatric lupus patients.

No uniform guidelines exist for the treatment of CNS lupus in childhood. Corticosteroids remain the mainstay of therapy. Adding monthly intravenous cyclophosphamide to high dose corticosteroids offered better control of severe CNS manifestations and may induce remission [39\*].

#### Pulmonary involvement

The frequency of respiratory system involvement in childhood lupus ranges from 5%-77%, depending on the series [2,40]. The clinical features are the same as those of adults, and pleural diseases are more common [2]. Restrictive lung disease is the most frequent alteration found by pulmonary function testing (PFT) in adult SLE patients [40]. Asymptomatic or subclinical lung involvement in juvenile SLE may be more prevalent than realized. Recently Trapani et al.[41] found 40% of a cohort of 15 children with lupus without clinical signs or symptoms, and without radiologic abnormalities, had a significant functional pulmonary impairment, including reduced diffusing capacity of the lung for carbon monoxide in 13%. The most frequent alteration in PFT was restrictive diseases, shown by reduced forced vital capacity and alveolar volume. This restriction in lung volume was thought to be secondary to interstitial changes rather than to reduced respiratory muscle strength because it was accompanied by decreased diffusing capacity of the lung for carbon monoxide. There were no significant changes in PFT after 1-year follow-up in this group. Furthermore, the investigators observed no correlation between pulmonary functional parameters and disease duration. No obvious correlation of PFT with disease activity was found, as measured by SLEDAI, other clinical manifestations, or any immunologic parameters except for a strong association of antibody to extractable nuclear antigens with forced vital capacity reduction [40]. The use of PFT as a screening tool in otherwise asymptomatic SLE children may be warranted for early detection of lupus lung involvement.

#### Osteoporosis in childhood systemic lupus erythematosus

Few studies suggesting the development of osteoporosis have been done in pediatric rheumatic diseases. Most were carried out in juvenile chronic arthritis populations [41\*\*]. Although the pathogenesis of osteoporosis is poorly understood, these contributing factors for children with SLE have been suggested: the duration of disease, severity of the inflammatory processes, the use of corticosteroids (both duration and daily and cumulative dose), limited exposure to the sun, and relative inactivity [41\*\*]. The major mechanisms of corticosteroid-induced osteoporosis include stimulation of osteoclastic bone resorption, decreased osteoblastic bone mineral deposition, and decreased intestinal absorption of calcium leading to mild secondary hyperparathyroidism [42\*]. Using dual energy X-ray absorptiometer to measure the lumbar spine bone mineral density (BMD), Trapani et al.[41\*\*] conducted the first longitudinal BMD study in pediatric SLE. Their population consisted of 20 childhood SLE cases and 31 healthy, age-matched control children matched for dietary calcium intake, activity level, and renal or endocrine diseases. A significant decrease in BMD was demonstrated in the peak bone mass period (aged 19-25 years) for patients compared to controls. There was a 3.4% decrease in the expected annual rate of increase in bone mass. The greatest loss in the rate of bone formation took place between 12 and 18 years of age. Disease activity measured by SLEDAI did not correlate with decreased BMD. When evaluating bone loss due to the use of

corticosteroids after one-year follow up, researchers found that the greatest bone loss occurred with the lowest cumulative steroid dose. As pointed out by the authors, this result agrees with the findings of others, because corticosteroids exert their greatest demineralizing effect in the first 6 months of use [41\*\*]. Efforts should be made to use the lowest possible dose of corticosteroids to maintain clinical efficacy. Several investigators have shown that regular exercise results in increased BMD in children [43,44].

Other clinical manifestations covered by Sandborg [4] in Current Opinion in Rheumatology (September 1998) will not be covered here.

#### Management

Corticosteroids remain the mainstay treatment of both pediatric and adult onset SLE. Management of disease in patients who do not respond to corticosteroid therapy remains a challenge. Antimalarials are widely used in children with lupus complicated by mild to moderate dermatologic and musculoskeletal manifestations. Antimalarial drugs lower the total serum cholesterol for patients who are on corticosteroids, but exert only a transient or minimal effect in the absence of corticosteroids. Rahman et al.[45\*] found that antimalarial drugs started before the use of corticosteroids reduced the hypercholesterolemia induced by steroids by 50%. Although it has not been demonstrated, these findings suggest the early initiation of antimalarial therapy for children with lupus on steroids may reduce the risk of premature atherosclerosis.

The effect of methotrexate was recently reported by Ravelli et al.[46] in a small series of 11 children with lupus. With the dose ranging from 12.5 to 17 mg/m<sup>2</sup>/week, the addition of methotrexate to oral corticosteroid therapy appeared to offer limited benefit. A potential role for oral cyclosporin is suggested by a recent report of its use in 30 adults with SLE [47]. Over a 2-year follow-up period, dramatic improvement was shown in clinical and laboratory parameters for patients both with and without lupus nephritis. However, disease activity recurred after discontinuation of cyclosporin. Stable childhood lupus nephritis with heavy proteinuria may also benefit from oral cyclosporin, as shown by Fu et al.[48]. Tacrolimus, another immunophilin binding agent, has induced remission in patients with severe cutaneous lupus vasculitis and panniculitis, which had not responded to multiple cytotoxic agents [49]. Autologous hematopoietic stem cell transplantation in severe SLE was recently reported by Burt et al.[50], with promising results. Two adult patients (one with severe renal disease and one with recurrent alveolar hemorrhage/diffuse proliferative renal disease) remained off immunosuppressive agents without disease progression or relapse 12 months post-transplantation. However, longer follow-up is required. The mechanisms of post-transplantation improvement are not well understood. Aggressive immunoablation prior to transplantation may destroy the "autoreactive clones" or may change the microenvironment of the immune system and modify the balance between self-tolerance and autoimmunity. Mittal et al.[51] report a lupus patient inadvertently given high dose cyclophosphamide (44.2 mg/kg intravenously) who remained in complete remission for almost 8 years.

#### Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome was first described in patients with SLE in 1987. The primary manifestations include arterial and/or venous thrombosis, thrombocytopenia, and recurrent fetal loss. Antiphospholipid antibodies (APAs)

are the leading cause of thromboembolic diseases in childhood, followed by factor V Leiden mutations [52]. APAs are a heterogeneous group of autoantibodies directed against negatively charged phospholipids that bind to plasma-protein cofactors, mainly prothrombin or [beta]2-glycoprotein 1. Lupus anticoagulants (LACs), detected by the prolongation of phospholipid-dependent clotting assays, and anticardiolipin antibodies (ACAs), measured by the reactivity to cardiolipin in solid-phase immunoassays, are the two major categories of APA. Male et al.[53] reported a retrospective study of 95 children who tested positive for LAC manifested by prolongation of activated partial thromboplastin time (APTT) assays and positive mixing tests. The majority (84%) were free of symptoms and the presence of LAC was found incidentally. None of the children who were initially free of symptoms had thromboembolic or bleeding complications after a median of 2.9 years follow-up. At follow-up after 1.9 years, APTT had normalized in 58% while 38% continued to have prolonged APTT (but did not fulfill all criteria for the presence of LAC) after 3.2 years. These studies indicate that LAC may be found transiently in otherwise healthy children without leading to complications. The finding of LAC after bacterial or viral infections has been described [53].

Literature regarding the link between APAs and thrombotic events in pediatric lupus is scarce, consisting primarily of anecdotal case reports. A recent cross-sectional study of APA and childhood SLE was conducted by Berube et al.[54]. This study included 59 children with lupus and an age-matched healthy control population. Assays to detect a LAC included a kaolin clotting time, an APTT, a diluted prothrombin time, and diluted Russell's viper venom time assays. The ACA isotypes and quantitation were determined by ELISA. In this cohort, 17% of children developed either venous or arterial thrombosis. Forty-one percent of these 59 patients had LAC, including 17% who were transiently positive (defined by the presence of one or more screening tests which were positive on one occasion only, with follow-up tests 3 months apart). Twenty-four percent of the children were persistently positive (one or more tests positive for APA on two occasions 3 months apart). The prevalence of ACA was 51% (30 of 59). Fourteen of 59 (24%) patients were persistently LAC-positive and 57% (8 of 14) of LAC-positive patients went on to develop one or more thrombotic episodes, compared to only 4% who were LAC-negative. It was found that children with SLE who were LAC-positive had a 28-fold increased risk of thrombotic events compared to their negative counterparts. Persistent positivity for ACA was detected in 19% of these patients, but there was no statistically significant association between the development of thrombotic episodes and ACA in this cohort. The most sensitive test for detecting LAC in pediatric lupus patients who went on to develop thrombotic events was diluted prothrombin time followed by APTT. Routine screening for LAC in children with SLE may be warranted. If positive tests persist on two or more occasions 3 months apart, counseling regarding the risk of thromboembolic events may be beneficial. The management of thromboembolic disease in the presence of APA in pediatric SLE currently follows the adult guidelines. Anticoagulation with heparin followed by coumadin is used in documented thromboembolic events but not in symptom-free LAC-positive children with lupus. The benefits of low dose aspirin as an antiplatelet agent are not yet clear.

#### Neonatal lupus

Neonatal lupus (NLE) is most often a transient, self-limited disease. However, congenital complete heart block is irreversible and is associated with a high morbidity and mortality [55\*]. Placental transfer of maternal autoantibodies against SSA/Ro and/ or SSB/La antigens during the second trimester is thought to

play an important role in the pathogenesis of tissue injury, but discordant twins suggest the involvement of other factors. Dermatologic, hepatic, and hematologic involvement are all transient and usually disappear at about age 6 months in parallel with the decline in maternal antibodies in the neonatal circulation [56\*]. Progress leading to better understanding of the pathogenesis of NLE has been summarized by Buyon in a recent review [56\*]. Data from both rabbit and human heart studies suggested the pathogenic role of anti-SSA/Ro, especially the 52 kD in inhibiting the L-type slow inward calcium channel, leading to reduction of the plateau phase of the action potential [56\*,57]. However, the experiments have not yet been tested on AV nodal tissue, which is more relevant to the clinical pathology of congenital heart block (CHB). It remains unclear why there is a sparing of the SA node in most NLE patients; involvement of the SA node is described in some NLE autopsies [56\*]. About half the mothers who give birth to an NLE infant are asymptomatic. The risk of giving birth to a child with CHB for a woman with anti-SSA/Ro and/ or anti-SSB/La is estimated to be 1-2%. The risk for mothers with primary Sjogren's syndrome might be higher [55\*]. Viana et al.[57], using a rabbit heart model infused with anti-SSA/Ro and/or anti-SSB/La sera, demonstrated that only one-third of the sera enriched with anti-SSA/Ro IgG induced cardiac conduction defects. All were directed against the 52 kD protein. In this model the titers of the anti-SSA/Ro antibodies did not seem to predict heart block despite previous reports that mothers of affected infants often had high antibody titers [55-57]. All anti-SSB/La positive sera did not produce cardiac conduction defects, nor did the sera from mothers with a previous obstetric history of NLE or that of healthy controls. These data suggest the prominent role of anti-SSA/Ro antibodies, especially the 52 kD subspecificity, in inducing such conduction defects and also that the time the samples are taken may effect the outcome of this experiment. Other as yet unidentified factors could contribute to the pathogenic effect of the autoantibodies. It is conceivable that the immune responses in both mothers and affected infants play a role in predisposing the neonatal heart to CHB. Recently, Siren et al.[58,59] reported two papers from Finland regarding the role of HLA in CHB. One study was conducted to identify the susceptibility alleles in mothers and the other to locate the susceptibility alleles in CHB children. Comparing mothers with SLE or Sjogren's syndrome who had diseased children with mothers with Sjogren's syndrome who had healthy children, researchers found that mothers with anti-SSA/Ro antibodies all have a strong association with HLA-B8/ DR3, the autoimmune-predisposing HLA alleles. However, mothers with HLA-A1, Cw7, B8 but B15 and positive for anti-SSA/Ro antibodies were at high risk of having CHB infants. Interestingly, no HLA class II deviation, which would suggest differences in autoantibodies in those mothers, could be demonstrated. Among the children, it was shown that particular HLA-DQ alleles might predispose to CHB, perhaps serving as antigen-presenting molecules on site. HLA-Cw3 is also involved and HLA-DRB, DQA and DQB antigens were often found to be identical in CHB children and their mothers. These antigens may affect fetomaternal recognition and cell-mediated immune responses involved in the pathogenesis of CHB [59].

Julkunen et al. conducted a retrospective study of obstetric history of 46 Finnish women with a CHB child, and compared the strength and specificity of anti-SSA/Ro and anti-SSB/La using ELISA and immunoblot assays [55\*]. The control groups comprised 85 women with SLE, 32 women with Sjogren's syndrome, and 89 normal women without CHB children. The familial incidence of CHB in this particular cohort was 6.2% and recurrence rate was 11.8%. As expected, CHB mothers had a history of more frequent fetal losses than did controls. Anti-SSA/Ro particularly against the 52 kD detected by immunoblot again indicated a higher risk of having a child with CHB. Although there was no antibody profile specific for mothers of diseased children, the combination of

anti-52 kD SSA/Ro by immunoblot and anti-48 kD SSB/La by immunoblot appeared to best identify mothers of children with CHB with sensitivity, specificity, and positive predictive value of 80%, 67%, and 52 respectively. Undetectable or low levels of antibodies by ELISA assays and no immunoblot reactivity indicated low risk. An interesting observation in this study was a higher prevalence of girls (64%) among the children with CHB.

Data reported by Buyon from the national registry as of May 1998 involved 187 mothers and their 222 affected children (142 with CHB alone, 49 with skin rashes alone by reports and 26 with both, 5 with liver and/or hematologic involvement) [56\*]. Of 87 pregnancies for which sufficient records were available, CHB without major anatomic defects was detected before 30 weeks of gestation in 71 (82%), with a median of 23 weeks. Pacemaker placement was required in 63% of live-born children (52% within 9 days, 22% within 1 year, and the rest after 1 year). Subsequent pregnancies led to delivery of CHB-affected children in 16%, and children with isolated rash compatible with NLE in 6%.

Mothers with CHB have a slightly increased risk of fetal loss [55\*]. About half of mothers of children with CHB eventually develop connective tissue disease but most cases have been mild and non-life-threatening [56]. No effective way exists to identify and prevent CHB, although we may be able to identify the high risk mothers, ie women with high titers of anti-SSA/Ro and anti-SSB/La, especially with anti-SSA/Ro by immunoblot, or women with primary SS or SLE, and mothers with previous CHB infants.

#### Drug-induced lupus

A number of medications have been reported to induce lupus-like syndromes, including hydralazine, procainamide, methyldopa, isoniazid, quinidine, chlorpromazine, anticonvulsants, and antithyroids. It has been suggested that certain determinations should be met before such diagnosis is made: there should not be any history suggestive of idiopathic SLE before the drug is started; a positive ANA should be detectable with at least one clinical feature of SLE while on the medication; and, importantly, rapid improvement in clinical symptoms with a gradual decline in ANA and other immunologic parameters should be entertained after the drug is discontinued [60]. Recent literature concerning drug-induced lupus (DIL) in childhood has focused on minocycline [61\*,62]. Minocycline has been increasingly used as part of acne therapy in young adults and to treat presumed Lyme disease. Minocycline-induced lupus has been reported primarily in young adults. It predominantly occurs in females who have been on the drug for periods of 10 days to 6 years [61\*]. Recently, Akin et al.[62] reported a series of five adolescent girls (age 14-17 years old) with minocycline-induced lupus-like syndrome. All had been treated with minocycline, for periods that varied from 6 weeks to 2 years, before DIL developed. The primary DIL manifestations included fever, fatigue, rashes, arthralgia/ arthritis, and hepatitis. The rashes could be urticarial or vasculitic in nature. Arthritis was usually symmetrical, nonerosive, polyarticular type involving small joints of the hands, wrists, knees and ankles. Hepatitis was characterized by increase in hepatic transaminases up to 10 times normal, which occurred in three of five patients. Laboratory findings included positive tests for ANA ranging from 1:80-1:640 (can be as high as 1:6400 [61\*]), but negative for anti-dsDNA. High sedimentation rate and positive anti-histone antibody (3/3) were also described. Two patients had positive p-ANCA but only one had low complement levels. Resolution of symptoms with improved serologic parameters after discontinuation of the antibiotic varied from 2 months to 4 months. One patient needed systemic

corticosteroids. Adolescent patients presenting with clinical symptoms suggestive of lupus, especially with hepatic involvement, should be questioned about minocycline exposure. Discontinuation of the antibiotic should result in recovery of both clinical and serologic parameters although oral steroid may be necessary.

Finkel et al.[63\*] reported a 9-year-old asthmatic girl who developed DIL after taking zafirlukast (Accolate, Zeneca Pharmaceuticals, Wilmington, DE), a leukotriene D4 receptor antagonist, at a dose of 20 mg twice a day for 8 days. The clinical manifestations were characterized by low grade fever, arthralgia/myalgia, proteinuria, mouth sore, and headache. Her ANA titer was 1:1280 with positive anti-histone antibodies to H2A-H2B histone-DNA complex and negative anti-DNA and anti-ENA. Her clinical symptoms were almost completely resolved with negative anti-H2A-H2B histone-DNA complex antibodies, 3 months after the medication cessation and without specific treatment.

### Conclusions

The outcome of childhood SLE continues to improve as improved access to medical care and diagnostic testing have provided better detection of children with SLE. Improved recognition of SLE and its complications is leading to earlier diagnosis and better management. Advances in understanding the immunopathogenesis of SLE, NLE, and related diseases over the past year include further identification of SLE susceptibility gene loci, and better understanding of the role of cytokines, immune-complex, and apoptotic cell clearance. Understanding the natural history of mothers and children with CHB has led to better counseling of further risk concerning the recurrence of CHB in subsequent pregnancies, although the exact immunopathogenesis remains unclear at this point. Managing children with complicated, recalcitrant lupus remains challenging. Autologous stem cell transplantation may be of benefit in such unfortunate patients but long term outcome is required to clarify the true benefit. Much remains to be learned regarding all aspects of SLE and its care.

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