Lupus nephropathy in children

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Introduction

Systemic lupus erythematosus (SLE) is a multifaceted disease in which kidney damage is an imposing clinical problem. Renal disease is very common occurring in 30–75% of patients [1,2]. Lupus nephritis is the major determinant of the long-term outcome of this disease [2]. Untreated, SLE has a significant mortality rate. On the other hand although the prognosis is improved dramatically with treatment, the nephrologist is faced with the task of balancing the toxic, prolonged, and complex treatment against the severity of the disease [3].

Pathogenesis

In SLE, the immune system is not able to generate an immune response that can discriminate between self and non-self antigens. B-cell dysregulation may be associated with alteration in T-cell function and subsets [1]. T-cell help for autoantibody production is hyperactive in SLE [1]. Genetic polymorphisms are important in these responses; certain MHC associations have been suggested to be associated with SLE [3,4]. Among these the haplotype HLA-A1, B8, DR3, and the silent C4AQ0 allele has been associated with lupus [5]. On the other hand, among non-HLA genes, individuals carrying specific genotypes for bcl-2, IL-10 have been shown to have a higher risk for developing lupus [4,6]. In human SLE, polymorphisms for TNF-α, IL-10, and Fc-γ receptor types IIa and IIIa have recently also been described as non-HLA susceptibility markers for the development of SLE [4].

Complement deficiencies are the best-known genetic associations of SLE. Congenital complement deficiencies are known to predispose for lupus [3]. Complement deficiencies of C2, C4, C1q and C1r, and SLE are the best-known genetic associations leading to SLE even in very young patients [4,5,7].

Both immune and non-immune mechanisms such as haemodynamic factors play a role in the pathogenesis of the renal disease in SLE. SLE nephritis is a prototype of immune complex-induced kidney damage. These immune complexes contain autoantibodies directed against nuclear and cytoplasmic constituents [1]. Anti-DNA antibodies have long been implicated in the development of lupus nephritis. However, recent reports have shown that the serum anti-dsDNA activity is always associated with antinucleosome reactivity [6]. Nucleosome presents the antigen composed of both dsDNA and histone. The nucleosome is a major auto-antigen that drives the T-cell-dependent autoimmune response [6]. In lupus nephritis, glomerular injury may result from either deposition of immune complexes, or from a direct cytotoxicity of pathogenic antibodies or in situ formation of complexes [1]. Autoantibodies may be against extracellular matrix proteins such as laminin or heparan sulfate as well. Once immune complexes are deposited, activation of the complement proteins leads to complement mediated damage which further activates other inflammatory mediators, procoagulant factors, releases cytokines and induces glomerular cellular proliferation and matrix synthesis [1]. Soto et al. [8] have shown that decreased apoptosis is also an important characteristic of proliferative lupus nephritis.

In membranous glomerulopathy, the binding of histones, or other autoantigens to glomerular subepithelial sites causing in situ immune complex formation may be the starting event. Histones and nucleosomes, which are cationic, have particular affinity for intrinsic negatively charged sites in the glomerular capillary wall, promoting planting of autoantigens [1].

In SLE, autoantibodies may be directed against other cellular components as well. We, and others, have shown that ANCA may also be pathogenic in lupus [9]. Among the other autoantibodies, antiphospholipid antibodies are important in the context of their role in the pathogenesis of thrombotic events in lupus [1,3]. The presence of antiphospholipid autoantibodies may lead to intravascular coagulation, promoting thrombotic glomerular and vascular lesions. Coagulation defects and non-immunogenic factors such as hypertension may also contribute to the glomerular and vascular damage in lupus nephritis.
**Clinical manifestations**

Throughout childhood the female/male ratio is 4.5:1, which is lower than 8–13:1 reported in adults [3]. Childhood lupus is often acute in onset. Revised ARA criteria in 1982 for the diagnosis of SLE is important. The presence of four or more of the ARA criteria gives a high sensitivity and specificity. Splenomegaly and lymphadenopathy are present in 1/4–1/3 of the children [3]. Many children with lupus are clinically anaemic and occasional children present with thrombocytopenia. Overt thrombosis should prompt a search for antiphospholipid antibodies [3].

Clinically significant renal involvement in SLE is common in children. Renal involvement in SLE is very diverse, ranging from asymptomatic urinary findings to nephrotic syndrome and even renal failure [10]. Overall 60–80% of children with SLE have abnormalities of the urine tests or of renal function early in their course and some develop renal abnormalities [3]. Most children with lupus nephritis present with proteinuria. Persistent microscopic haematuria is common. Hypertension has been reported in 40%, and half of them have been reported to have a reduced renal function [3]. In a review of 49 children with SLE, 27 patients had a glomerular filtration rate of less than 65 ml/min and/or proteinuria of greater than 2.5 g/day [11].

In a retrospective analysis of the 71 patients in our centre, clinical and laboratory features of kidney disease were present in 64.8% of the patients. A quarter (25.4%) of these have presented with renal failure and 25.4% had hypertension. These results are compatible with those in the literature on paediatric lupus.

**Pathology**

An important aspect of lupus nephritis is its very pleomorphic character. The disease carries the potential to progress over time [1,3]. Furthermore pathological findings may not always correlate with the clinical manifestations. Therefore, biopsy is a crucial procedure for planning effective therapy.

The recent World Health Organization classification for lupus nephritis includes six histopathological groups (Table 1).

Activity and chronicity indices are useful for clinical judgment and treatment [10]. High chronicity index correlates with a poor prognosis in these patients.

**Table 1. Classification of lupus nephritis [1]**

<table>
<thead>
<tr>
<th>I:</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>II:</td>
<td>Mesangioiopathic glomerulonephritis</td>
</tr>
<tr>
<td>III:</td>
<td>Focal and segmental glomerulonephritis</td>
</tr>
<tr>
<td>IV:</td>
<td>Diffuse proliferative glomerulonephritis</td>
</tr>
<tr>
<td>V:</td>
<td>Membranous glomerulonephritis</td>
</tr>
<tr>
<td>VI:</td>
<td>Chronic sclerosing glomerulonephritis</td>
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</tbody>
</table>

Pathological findings are not confined to the glomerulus. Tubulointerstitial disease and vascular diseases are also well recognized [1].

**Treatment**

In the treatment of lupus nephritis there are two major problems. The first is the acute treatment of severe life-threatening disease. The second is the long-term management of chronic, indolent disease [3]. Class I and II lupus nephritis represent mild renal lesions and it is accepted that they do not require specific therapy apart from the treatment of the disease itself [10]. However, as they may progress to more severe disease one has to follow the patients carefully.

Class III nephropathy is a focal and segmental glomerulonephritis. Niaudet [10] has suggested that no specific treatment is indicated if only 20% of the glomeruli are affected associated with mild clinical findings. However, if more than 40% of the glomeruli are involved with necrosis and deposits, he has suggested aggressive treatment such as for Class IV nephritis [10].

Class IV patients have diffuse proliferative glomerulonephritis and are those who require aggressive immunosuppressive treatment. Others have suggested intravenous (i.v.) corticosteroids, followed by oral prednisone along with oral cyclophosphamide for 3 months [3]. A number of studies have advocated i.v. cyclophosphamide as monthly pulses 500–1000 mg/sqm, to be superior to oral cyclophosphamide [3,12,13]. Cyclophosphamide pulses are given for at least 6 months and in some centres are continued every 3 months for 2 years [10–13]. Lehman and Onel [14] have reported excellent results with i.v. cyclophosphamide therapy in 16 children with lupus nephritis, 11 of whom had Class IV nephritis. The cyclophosphamide boluses were switched to every 3 months after the initial monthly 6 pulses. The treatment was continued for 36 months with oral prednisone [14]. However, a meta-analysis has failed to confirm the superiority of pulse cyclophosphamide over oral cyclophosphamide [12]. Patients who are treated with oral cyclophosphamide are switched to oral azathioprine after the completion of oral cyclophosphamide treatment [10]. Oral cyclophosphamide is given at a dose of 2 mg/kg/day, which should be reduced to 1 mg/kg/day in the presence of renal insufficiency [3].

Other treatment modalities such as mycophenolate mycophenolate (MMF), cyclosporin, and FK506 have been reported with success in selected cases [15]. However, long-term controlled studies in children are not available for comparing these treatment modalities. A multicentre trial of MMF has recently been started. Although uncontrolled studies have shown that plasmapheresis may be favourable, controlled trials have shown that the addition of plasmapheresis to immunosuppressive treatment does not introduce any additional benefit [15]. It should, however, be considered in the acute treatment of severe resistant...
disease. Experimental therapy such as CD40 ligand blockade is also being assessed. Bone marrow transplantation has been tried in very resistant cases with varying success.

Treatment of Class V nephritis is controversial. Although specific treatment is not routinely suggested, protocols involving cyclosporin, pulse steroids, and chlorambucil have been used [10]. A 6-month regimen consisting of corticosteroids (three pulses followed by oral prednisone 0.5 mg/kg/day) during months 1, 3, and 5 and chlorambucil (0.2 mg/kg/day) for months 2, 4, and 6 has been suggested [10]. Patients with pure membranous nephropathy, or mild proteinuria have a good prognosis.

Detailed attention should be paid to optimize treatment since in childhood problems with growth, psychosocial development, and gonadal toxicity are important issues.

Prognosis

Class IV nephritis has the most severe prognosis and is at high risk of progression to end-stage renal disease, particularly in those patients with extensive crescent formation and necrotizing glomerular lesions [3]. Other poor prognostic factors in SLE include hypertension, male sex, poor socioeconomic status, black race, initial high serum creatinine, presence of antiphospholipid antibodies, and high overall disease activity [10]. For those who progress to end-stage renal failure, renal transplantation is the treatment of choice [10]. Disease activity usually declines after transplantation.

References