Recent advances in the management of Pediatric Lupus Nephritis.

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MAGNITUDE OF THE PROBLEM

Around 15 to 20% of SLE begins before the age of 19 years. Childhood-onset SLE (cSLE) is a rare disease with an incidence of 0.3-0.9 per one lakh children-years and a prevalence of 3.3-30.4 per 100,000 children. (1, 2)

Data from India are limited to case series. Comparison of these case series to cohorts of Caucasian cSLE from the west illustrates that Indian cSLE patients may have onset of disease at a younger age, lesser female predominance, much more likely to have fever and positivity for dsDNA as well as less likely to have cutaneous involvement (esp. patients from south India). The prevalence of arthritis, and major organ involvement was comparable between the two. (3) Similar findings have been replicated when comparing Indian/South Asian (migrant) pediatric lupus patients with caucasian patients in a multi ethnic cohort. (4)

Among the major organ involvement none is dreaded as much as renal involvement. Renal involvement is much more common in children compared to adult. Case series and retrospective data have demonstrated that from 50 to 90% of children with SLE can develop
lupus nephritis during the entire course of their disease. Most of the children who do develop the disease do so within 2 years of disease onset. (1, 2)

In this review an attempt is made to predominantly focus on recent advances as well as paradigm changes that have occurred and potential evidence for future paradigm changes that are likely to occur in children with lupus nephritis. For a more basic and comprehensive review on all aspects of pediatric lupus nephritis readers are referred to two very good reviews published in the last couple of years. (5, 6)

THE DIAGNOSIS

In order to ensure prompt institution of appropriate therapy (to prevent long term permanent damage) it becomes imperative for the treating doctor to diagnose lupus nephritis in a timely manner and stage them correctly. Histopathology of the kidney biopsy specimen is the gold standard method for diagnosis and staging of lupus nephritis. Performing a kidney biopsy is essential as there can be many causes other than lupus nephritis, which could be responsible for urinary abnormalities or azotemia in a child with lupus. (See table 1)

Table 1. List of differential diagnosis for lupus nephritis

<table>
<thead>
<tr>
<th>Proteinurias related to stressful conditions</th>
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<tbody>
<tr>
<td>Fever</td>
<td></td>
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<tr>
<td>Seizure</td>
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Infections

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Urinary tract infections</th>
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<tbody>
<tr>
<td>Group A beta-hemolytic streptococcus infection, (post streptococcal glomerulonephritis)</td>
<td></td>
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</tbody>
</table>
Viral infection | Hepatitis B
| Infectious mononucleosis

Others | Malaria

**Medications**

| Antibiotics | Cephalosporins, Macrolides, Penicillins, |
| Diuretics | Furosemide, Thiazides, |
| Miscellaneous | Proton pump inhibitors |

There are no pediatric specific criteria to help in suspecting lupus nephritis and deciding to proceed with a kidney biopsy. A recent survey of pediatric rheumatologists and pediatric nephrologists in North America showed that only 28.8% of surveyed specialist follow the American college of Rheumatology (ACR) guidelines(7) for renal biopsy in a patient with suspected lupus nephritis (See figure 1). Isolated hematuria and isolated proteinuria were considered sufficient grounds for biopsy according to 25% and 58.2% of specialists (respectively). Four of the 182 pediatric sub-specialists surveyed, routinely recommend or perform kidney biopsy in all newly diagnosed pediatric SLE patients. (8) There is no data either observational or survey based from India regarding the criteria used for performing kidney biopsy in children with suspected lupus nephritis. However, it is probable (based on the personal experience of the author) that Indian pediatricians and specialists are likely to be much more conservative with respect to performing a biopsy than our North American / Western colleagues. The largest study of Indian children with lupus nephritis published from PGI Chandigarh revealed that only 53 out of 72 children with lupus nephritis were subjected to renal biopsy. (9)Adult SLE data from SGPGI lucknow, has demonstrated that among the retrospective cohort of 188 patients with lupus nephritis, 53 patients who were not biopsied had a worse renal survival than patients with Class III or Class IV lupus nephritis. (10)
<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial</td>
<td>Normal by light microscopy but mesangial deposits by IF</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative</td>
<td>Mesangial hypercellularity, mesangial matrix expansion with mesangial immune deposits. No subepithelial or endothelial deposits by light microscopy</td>
<td>Mainly Asymptomatic, sometimes Hypertension</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal</td>
<td>Focal segmental or global endo or extra capillary GN involving &lt;50% with focal subendothelial deposits</td>
<td>Asymptomatic OR Nephritic syndrome</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse</td>
<td>Diffuse segmental or global endo or extra capillary GN involving &gt; 50% with diffuse subendothelial deposits</td>
<td>Nephritic syndrome, Nephrotic syndrome, Hypertension</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous</td>
<td>Global or segmental subepithelial deposits</td>
<td>Nephrotic syndrome, Hypertension</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerosing</td>
<td>&gt; 90% of glomeruli globally sclerosed</td>
<td></td>
</tr>
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</table>

Table 2 Classification of lupus nephritis

When international guidelines as well as data from Indian cohorts (atleast from adults) are so clear about the need for performing biopsies then why is it that we generally tend to hesitate to perform biopsies? It is predominantly due to risk of complications, chief among them is bleeding. Complications including major complications such as prolonged gross hematuria and large perinephric hematoma is known to occur between 0–14 % of children after kidney biopsy procedure. When routine ultrasonography was performed 2 weeks after kidney biopsy upto 40% of children were seen to have intra-renal or peri-renal hematomas. However, most of them resolved spontaneously.
In the adult SLE cohort from SGPGI referred to earlier, the most common cause of lack of biopsy was refusal of consent by the patient (~50%). However the next most common cause cited was thrombocytopenia (~20%). (10) Thrombocytopenia does seem to predict complications in renal biopsy. A retrospective study of 219 SLE patients who underwent renal biopsy in John Hopkin’s institute demonstrated the risk for major complication increased by 27% for every 10,000 cells/mm³ decrease in platelet count. A platelet count of < 150,000 cells/mm³ seemed to confer a 30 times higher risk of major complication. Thus, despite a platelet count of > 50,000/mm³ being the usual criteria considered safe by clinicians for biopsies and other invasive procedures (and in fact this was the cut off used in the John Hopkin’s protocol), it would seem more prudent to consider a more stringent criteria of > 150,000/ mm³ in SLE patients planning to undergo a kidney biopsy. (14) Another major predictor of complication during renal biopsy for SLE patients that has emerged in recent time is the presence of anti phospholipid antibody syndrome. A retrospective cohort from St Thomas’ hospital in London included 215 biopsies performed in 199 patients. Patients were divided into three groups, SLE alone, SLE with antiphospholipid antibody syndrome, and a third group of SLE patients with antiphospholipid antibody test positive (but not the syndrome). The rates of major bleeding were 1%, 11%, and 8%, respectively. A persistently positive Lupus anticoagulant (LAC) was associated with significantly increased the risk of bleeding complications (odds ratio [OR] 3.32, P = 0.03). Hence, along with a more stringent platelet count criteria, all lupus nephritis patients should in all probability be checked for anti phospholipid antibodies before undergoing renal biopsy. (15)

Given the risk of complications there has ongoing work to determine less invasive tests and biomarkers to diagnose lupus nephritis. Based on data from pediatric SLE patients from the John Hopkin’s cohort a few clinical characteristics emerged as predictive of the presence as well as future development of lupus nephritis. All male children in the cohort developed lupus nephritis. Not surprisingly the presence of low serum albumin as well as positive dsDNA was predictive of the presence of kidney disease. However in longitudinal analysis, low serum albumin (hazard ratio 3.4) (along with isolated sterile pyuria, hazard ratio 3.0) was associated were predictors of future kidney disease. This implied that children with low serum albumin or sterile pyuria at baseline were three times more likely to develop lupus nephritis during the period of follow up. Patients with these findings need to be monitored.
more closely for the possible development of lupus nephritis. The presence of anti Ro antibody was protective against the development of lupus nephritis. (16) There has been interest for considerable period of time in Urinary biomarkers for the prediction and staging of renal disease in lupus patients. The most potentially promising candidates have been urinary neutrophil gelatinase associated lipocalin and urinary monocyte chemoattractant protein 1. (17) The same has been recently validated in pediatric patients as well. (18) Certain urinary biomarkers such as 1-acid-glycoprotein, lipocalin-type prostaglandin D-synthetase are particularly useful only in pediatric patients since they are found to be increased in diabetic renal disease as well. In the study by Suzuki et al urinary levels of transferrin, 1-acid-glycoprotein, lipocalin-type prostaglandin D-synthetase were significantly increased 3 months prior to a clinical flare of lupus nephritis. (19)

The classification of renal involvement and accompanying clinical features are outlined in table 2. Class III (focal proliferative) and Class IV (diffuse proliferative) lesions are the most frequent and severe lesions, forming more than 80% of cSLE biopsies.

**THE TREATMENT**

It is disheartening to note that there is an absolute lack of good prospective randomised control trials for pediatric lupus nephritis. Most of the treatment protocols have been directly adopted from recommendations in adults. The EULAR-EDTA recommendations for the treatment of lupus nephritis state: “pediatric LN diagnosis, management and monitoring are similar to that of adults”. (20) However this seems to be more of an expert opinion of the panel members, than based on actual evidence. As reviewed below, the treatment paradigms and outcomes in adults can not be assumed to be exactly reproducible in children. Children can not, and should not, be viewed as small adults.

Since pioneering work by Boumpas et al (21) in the 1990s it has become very clear that corticosteroids can not be used as as the sole agent in patients with lupus nephritis. Recent evidence gained regarding the use of the four main immunosuppressive agents being used for the management of pediatric lupus nephritis are outlined below.
Cyclophosphamide

As part of the CARRA consensus treatment protocol preparation, an initial Delphi survey of participating pediatric rheumatologists was conducted. The survey demonstrated that 79% of the respondents prescribe cyclophosphamide as an immunosuppressant in lupus nephritis. (22) Initial data which emerged from case series of children with lupus nephritis does seem to support the doctors' enthusiasm regarding this agent. Lehman and Onel from USA reported 16 children with lupus nephritis treated with 3 years of IVCY, who underwent rebiopsy after completion of the course. The renal biopsy activity index significantly improved (p < 0.001) along with the proteinuria and mean creatinine clearance. (23) Retrospective cohort data from 1974 to 1999 of 33 pediatric patients with lupus nephritis in a single centre in Italy was published a few years later. Nineteen children who received only corticosteroids and azathioprine were compared to the other 14 who received cyclophosphamide. Patient in the cyclophosphamide group seem to have better patient and renal survival and more importantly less growth impairment.(24)

However subsequent data were less positive. Nine arab children reported by Al Salloum et al. showed improvement during Cyclophosphamide treatment but 56% progressed to chronic renal failure 2 years after discontinuation of therapy. (25) Even in the larger 48 patient cohort reported from Thailand recently, long term remission was not at all common. (26)

Differential response to cyclophosphamide based on ethnicity could also be one of the reasons for these disappointing results in some series. This was shown in the secondary analysis of the Aspreva Lupus Management Study (ALMS) trial as well. (27) Another reason could be due to difference in doctors perceived preference and actual usage in real life. A publication by the PRINTO collaborative group involving centres in Argentina, Costa Rica, Brazil, Turkey, Canada and Italy analysed treatment pattern for children diagnosed with lupus nephritis (or those who flared) between 2001 and 2004. Surprisingly only 44.1 % of the patients were treated with cyclophosphamide. (28) The EULAR-EDTA recommendations also seem to suggest that the low dose Euro lupus nephritis treatment (ELNT) protocol be used for treatment of Class III and Class IV lupus nephritis in children as well.(20) However, there are no reports attesting to its efficacy in children. The equivalent dose in children and whether that dose will vary according to the age and body surface area of the child is
uncertain. Nor is there any evidence that the ELNT protocol is as good as standard dose monthly cyclophosphamide in children.

Despite these caveats, as stated earlier, cyclophosphamide remains one of the most preferred options for the treatment of pediatric lupus nephritis. The reason is evident in the Delphi survey by the CARRA group. Physicians said that their choice of the immunosuppressive medication was influenced by co-existent morbidities, especially lupus cerebritis (81%), and the fear of non-adherence (87%). (22)

**Mycophenolate mofetil (MMF)**

Based on studies in adult patients, from the advent of the 21st century MMF is increasingly being used in children. Initially encouraging case reports were published of its use in patients resistant to Cyclophosphamide. (29,30)

Based on these encouraging reports it increasingly has become the 'go to' drug in patients with pediatric lupus nephritis. One of the largest comparison of outcomes between pediatric lupus nephritis patients treated with cyclophosphamide and MMF was published in 2011. In the large retrospective cohort data from Holtz Children’s Hospital, in Miami, USA, the outcomes of 138 patients between 1980 and 2001 stratified as per treatment protocol were compared. MMF was used for induction and maintenance in 31 children. The median renal survival time was 12 years compared to 6 years among 24 patients treated with 36 month NIH cyclophosphamide protocol. (p<0.01). The 5-year absolute renal survival was 91% in MMF group compared to 52% in the cyclophosphamide group. (p<0.01) (31)

Subsequent publications have shown the MMF is also quite an effective agent for maintenance of remission and probably more effective than azathioprine. (32,33,34)

**Rituximab**

Rituximab has commonly been used by clinicians for both renal and non renal manifestations of lupus. However the EXPLORER (35) and LUNAR (36) trials, randomised controlled
trials for the use of rituximab in non renal and renal manifestations of lupus (respectively), were negative trials. The trial design including the excessive use of steroids was blamed for the disappointing results.

Inspite of the negative results from these two trials, clinicians continued to believe that rituximab was effective in patients with lupus. Publications of retrospective case series continued to suggest that rituximab is effective in the treatment of lupus nephritis. (37) In fact both the American college of rheumatology (7) as well as the EULAR guidelines (20) for the management of lupus nephritis continued to recommend rituximab as add on or as monotherapy in lupus nephritis patients with resistant disease. Pediatric retrospective case series in children also demonstrated the rituximab is effective in pediatric lupus nephritis patients. (38,39)

However the retrospective review in the Holtz children’s hospital cohort in Miami failed to demonstrate any improvement in renal survival in patients treated with Rituximab compared to patients treated with MMF. (31)

Not too long back, the lupus world was thrown into a tizzy with the publication of the RITUXILUP study where a prospective single centre observational adult cohort with lupus nephritis were treated with combination of rituximab and MMF without any daily oral steroids. (40)

Thus rituximab does appear to have a definite role in lupus nephritis. However our understanding of the niche position it occupies in the therapeutic armamentarium for lupus nephritis seems to still be in an evolving phase. This understanding is still in its infancy in children.

**Calcineurin inhibitors**

Cyclosporine has been used for the treatment of lupus nephritis since quite some time particularly in patients with stage V lupus nephritis. (41)
However recent evidence from prospective trials as well as retrospective cohorts have shown encouraging data for the use of Tacrolimus in not only resistant patients (both as alternative and as add on therapy) but also as first line agent for remission induction. Tacrolimus is a more effective calcineurin inhibitor than cyclosporine and has a much better safety profile. In an open label three arm 24 week prospective randomised trial in which 60 adult patients with lupus nephritis were enrolled tacrolimus was compared to MMF and cyclophosphamide for remission induction. Tacrolimus was not only comparable to MMF induction efficacy (and better than Cyclophosphamide) but also seemed to lead to faster resolution of proteinuria and also much safer in terms of to the number of the infections in the cohort. (42)
Subsequently, long term data on the use of tacrolimus has also shown encouraging . Tacrolimus appears to be comparable to MMF for both induction as well as maintenance. (43,44). A few case studies in pediatric lupus nephritis (predominantly from a single centre in Japan) seem to demonstrates it’s efficacy (and safety) in children as well.(45)

What makes the use of calcineurin inhibitors significantly attractive is the finding that resistance to glucocorticoids (and possibly other immunomodulators) in autoimmune disease is modulated by the action of a transmembrane protein called P-glycoprotein. Calcineurin inhibitors are able to block the action of glycoprotein P and hence one of their main modes of action maybe to help in overcoming resistance of autoimmune diseases to steroids ( and other immunomodulators) (46) Probably due this ability of tacrolimus to overcome drug resistance it is being tried as add on therapy for patients with lupus nephritis on corticosteroids and MMF. The few case reports and case series for this mode of “multi-targeted therapy” are encouraging. (47,48,49,50)

**Other medications**

Other medications such as ocrelizumab and epratuzumab, cladribine, fludarabine, belimumab, epratuzumab, atacicept, abetimus,infliximab, tocilizumab, eculizumab, belatacept, abatacept,sirolimus, and rigeromid which have been used for lupus nephritis are reviewed in brief elsewhere. (5)

**Protocol**
The EULAR-EDTA guidelines(20), the ACR guidelines (7), the CARRA consensus treatment plan (22) as well as available evidence in children have been used to prepare a flow chart to aid clinical decision making for induction therapy in childhood lupus nephritis figure 1. The drug of choice for maintenance therapy is again MMF. For the maintenance phase, MMF can be used at a lesser dose of 400-800 mg/m2/day in two divided doses. The patient should be continued on very low dose steroids during the maintenance phase. The duration of treatment is for a minimum of 3 years after which steroids may be stopped before tapering or stopping of immunosuppressive therapy is considered.

**Adjunctive therapy**

An important aspect of therapy is that clinicians need to taper steroids as soon as possible and use the least possible dose. Recent data demonstrates that in the long run, organ damage, as well as cardiovascular morbidity and mortality in SLE is significantly linked to steroids use and hence in adults a daily dose of >6mg/day is considered “too high”. In children, due to lack of data, this may be assumed to represent a limit of 0.1mg/kg/day.

Blood pressure control ideally using optimal blockage of renin-angiotensin system using angiotensin converting enzyme inhibitors as well as angiotensin receptor antagonists are essential not only to control hypertension but also to reduce proteinuria.

Most guidelines stress that baseline HCQS should be given to all patients with lupus nephritis. Not only does it reduce other manifestation of lupus but also reduces the risk of renal flares, reduces associated dyslipidemia, reduces infection risk, helps reduce the risk of thrombotic events and premature atherosclerosis. (51)

Adolescents and children with lupus nephritis do tend to develop cardiovascular disease. Though the absolute risk may be low the relative risk is very high compared to other children of the same age group. Judicious use of statins despite the negative findings of the APPLE trial are still justified. In fact a secondary analysis of the results of the APPLE study seems to suggest the efficacy of atorvastain in patients with higher CRP. (52)

The causes of death was equally distributed between vascular events, cancer, infection,
and renal failure in adults with lupus nephritis. The majority of deaths among most pediatric cohorts was due to infection. (between 50 to 62.5%). This can be prevented not only by reducing the dosage of daily steroids but also by immunisation. (54)

CONCLUSIONS

The pediatric lupus nephritis data from PGI seems to suggest that children in India fare much worse compared to the children reported in literature from western countries as well as from other asian countries. With the help of new data demonstrating predictors of complications (platelet count <1,50,000/cmm and presence of antiphospholipid antibody syndrome) we can be less apprehensive about performing kidney biopsy. Taking into account the findings by Varun Dhir et al, early and more routine biopsies may itself translate into better care and better outcomes in our patients. MMF seems to the preferred choice of therapy with cyclophosphamid being a reasonable alternative therapy paricularly when compliance is doubtful. Data regarding rituximab and tacrolimus seem to be encouraging. Combinations and multi targeted therapy may offer more effective and less toxic treatment paradigms in the future as evidenced in the RITUXILUP trial in adults. Adjuctive therapies including immunisation need to be kept in mind to improve patient outcomes.

References


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