Management of steroid dependent and steroid resistant Nephrotic syndrome in children

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ABSTRACT

Nephrotic syndrome is a common pediatric kidney disease which is characterized by the leakage of the protein from the blood into urine through the damaged glomeruli. Nephrotic syndrome is characterized by heavy proteinuria, hypoalbuminemia (serum albumin <2.5 g/dl), hyperlipidemia (serum cholesterol >200 mg/dl) and edema. Nephrotic range proteinuria is present if early morning urine protein is 3+/4+ (on dipstick test), spot protein/creatinine ratio >2 mg/mg or >200 mg/mmol urine albumin excretion >40 mg/m² per hour. Precise quantitative measurement is necessary by 24 h urine protein measurement. Nephrotic syndrome can affect children of any age, from infancy to adolescence and is most commonly seen among school-aged children and adolescents. The prevalence worldwide is approximately 16 cases per 100,000 children with an incidence of 2 to 7 per 100,000 children. (1) Males appear to be more affected than females at a ratio of 2:1 in children, but this predominance fails to persist in adolescence. Originally, there is a recommended regimen comprising of 4-5 weeks each of daily and alternate day steroid therapy. Prolongation of initial steroid therapy for 12 weeks or longer is associated with significantly reduced risk for subsequent relapses; prolonged treatment with steroids is associated with a higher frequency of adverse events. For management of initial episode of nephrotic syndrome steroidal therapy is sufficient. For the management of steroid dependent nephrotic syndrome combination of steroidal therapy and immunomodulators are necessary. For management of steroid resistant therapy along with steroids and immunosuppressant’s, ACE inhibitor drugs, HMG COA inhibitors and diuretics should also be included.

Key words: Nephrotic syndrome, proteinuria, immunomodulators, prednisolone, levaamisole, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil.

INTRODUCTION

Nephrotic syndrome is a manifestation of glomerular diseases characterized by nephritic range proteinuria, hypoalbuminemia, hyperlipidemia and generalized edema. This is seen in Table 1 (Srivastava et al., 1975)

EPIDEMIOLOGY

Occurs at all age groups but mostly common in children of one year five months to six years with a ratio of 2:1(Boys>Girls). It is higher in underdeveloped countries and the incidence worldwide records 2-7 cases per 100,000 children /year (Kerlin et al., 2012).

MANAGEMENT OF INITIAL EPISODE

Appropriate therapy at the first episode is an important determinant of the long term course of the disease. Prednisolone is the drug of choice and it is given at a dose...
Table 1: Characteristics of nephritic syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>Nephrotic range proteinuria</td>
<td>• Early morning urine protein is 3+/4+ (on dipstick boiling test)</td>
</tr>
<tr>
<td></td>
<td>• Spot protein/creatinine ratio &gt;2mg/mg</td>
</tr>
<tr>
<td></td>
<td>• Urine albumin excretion &gt;40mg/m²/hr on a timed sample</td>
</tr>
<tr>
<td></td>
<td>• Urine protein excretion ratio &gt;50mg/kg/24hr</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>• Serum albumin &lt;2.5g/dl</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>• Serum cholesterol &gt;200mg/dl</td>
</tr>
<tr>
<td>Generalised edema</td>
<td></td>
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</tbody>
</table>

Table 2: Initial treatment of steroids

<table>
<thead>
<tr>
<th>Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Urine albumin nil or trace (or proteinuria &lt;4 mg/m²) for 3 consecutive early morning specimens.</td>
</tr>
<tr>
<td>Relapse</td>
<td>Urine albumin 3+ or 4+ or proteinuria 40 mg/m²/hr for 3 consecutive early morning specimens, being on remission previously.</td>
</tr>
<tr>
<td>Frequent relapses</td>
<td>Two or more relapses in initial six months or more than 12 relapses in initial twelve months</td>
</tr>
<tr>
<td>Infrequent relapses</td>
<td>Three or less relapses a year</td>
</tr>
<tr>
<td>Steroid dependence</td>
<td>Two consecutive relapses on alternate day steroids or within 14 days of its discontinuation.</td>
</tr>
<tr>
<td>Steroid resistance</td>
<td>Failure to achieve remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for 4 weeks.</td>
</tr>
</tbody>
</table>

TREATMENT OF RELAPSE

Relapse is defined as urine albumin 3+ or 4+ or proteinuria 40 mg/m²/hr for 3 consecutive early morning specimens, being on remission previously. An URTI or some other infection usually precipitates a relapse. Prednisolone is administered at a dose of 2 mg/kg/day until urine protein is trace or nil for three consecutive days. Subsequently prednisolone is given in a single morning dose of 1.5mg/kg on alternate days for 4 weeks and then discontinued (Westhoff et al., 2006). Infrequent relapses can be defined as initial responder with three or less relapses a year managed using prednisolone regimen.

MANAGEMENT OF STEROID DEPENDENCE FREQUENT RELAPSES

Frequent relapses are defined as two or more relapses in initial six months or more than three relapses in initial twelve months. Steroid dependence is defined as occurrence of two or more consecutive relapses when on alternate day steroids or within 14 days of discontinuation. Prednisolone is gradually tapered to maintain the patient on remission on alternate day dose of 0.5-0.7 mg/kg. A close monitoring on growth, blood pressure and steroid toxicity should be observed. If there is no steroid toxicity with prednisolone 0.5-0.7mg/kg on alternate days then continued for 9-18 months (Afzal et al., 2007). If there is any associated steroid toxicity, addition of the following immunomodulators is suggested; Levamisole, Cyclophosphamide, Cyclosporine, Tacrolimus, Mycophenolate mofetil.

Levamisole

Levamisole is an immunostimulant drug that enhances the Th1-mediated immune response and reciprocally down regulates the Th2 lymphocyte-mediated immune response. A dosage of 2-2.5 mg/kg on alternate days for 12-24 months is required. Prednisolone dose is gradually tapered to 0.25-0.5 mg/kg for a period over 8 months. Significant adverse reactions are agranulocytosis, skin rash and febrile illness. They occur in a small subpopulation of patients only, predominantly those with rheumatoid arthritis. Leucocyte count should be monitored every 2-4 months (Afzal et al., 2007).

Cyclophosphamide

Cyclophosphamide is an immunostimulant drug. The dosage and duration of the drug is 2-2.5 mg/kg/day for 12 weeks and it should be started following remission of proteinuria. Prednisolone dose is gradually tapered to 1 mg/kg for a period over 6 months and then stopped. The adverse reactions of the drug include Hemorrhagic cystitis,
Table 3: Treatment for steroid resistant nephritic syndrome

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>REMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine and prednisolone</td>
<td>4-6mg/kg/day in two divided doses for 2-3 years</td>
<td>50-80 %</td>
</tr>
<tr>
<td>Tacrolimus and prednisolone</td>
<td>0.12-0.15mg/kg/day in two divided doses for 2-3 years</td>
<td>70-85 %</td>
</tr>
<tr>
<td>Oral cyclophosphamide and prednisolone</td>
<td>2-3mg/kg/day for 12 weeks</td>
<td>25-30 %</td>
</tr>
<tr>
<td>Iv cyclophosphamide and prednisolone</td>
<td>500-750mg once every month for 6 months</td>
<td>40-65 %</td>
</tr>
<tr>
<td>Iv methylprednisolone, cyclophosphamide and prednisolone</td>
<td>20-30mg/kg for 6 alternate day, then once a week for 8 doses, fortnightly for 4 doses, once a month for 8 doses.</td>
<td>40-70 %</td>
</tr>
</tbody>
</table>

alopecia, nausea, vomiting, gonadal toxicity. Leucocyte count should be monitored every 2 weeks, discontinued if falls below 4000 mm3. Use of more than 12 weeks should be avoided because of gonadal toxicity (Afzal et al., 2007; Bagga et al., 1999).

Calcineurin inhibitor: Cyclosporine

Cyclosporine is an immunosuppressive drug with a dosage of 4-5mg/kg daily for 12-24 months. Prednisolone dose is gradually tapered to 0.25-0.5 mg/kg for a period over 8 months and then stopped. The adverse effects include hypertension, gum hypertrophy, hirsutism, nephrotoxicity, tremors, restlessness, stomach upset, nausea, cramps, diarrhea, headache, and changes in blood sugar. Plasma CsA levels should be monitored every 2-3 months and lipid profile is checked annually. Repeat kidney biopsy to examine for nephrotoxicity if duration of treatment extended above 2 years (Afzal et al., 2007; Bagga et al., 1999).

Tacrolimus

Tacrolimus is an immunosuppressive drug with a dosage of 0.1-0.2 mg/kg daily for 12-24 months. Prednisolone dose is gradually tapered to 0.25-0.5mg/kg for a period over 8 months and then stopped. Its adverse effects are Hyperglycemia, diarrhea, neurotoxicity. Serum creatinine and glucose is monitored every 2-3 months. Repeat kidney biopsy to examine for nephrotoxicity if duration of treatment extended above 2 years (Afzal et al., 2007; Bagga et al., 1999).

Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressive drug with the dosage of 800-1200 mg/day daily for 12-24 months. Prednisolone dose is gradually tapered to 0.25-0.5 mg/kg for a period over 12-24 months. GI discomfort, diarrhea, leucopenia are usually the adverse effect of the drug. Leucocyte count should be monitored every 2 weeks, discontinued if falls below 4000 mm3 (Afzal et al., 2007; Bagga et al., 1999).

Choice of immunomodulator

First choice is Levamisole or cyclophosphamide. Cyclophosphamide is preferred in patients showing a poor compliance or difficult to follow up. Relapses occurring during immune modulator therapy must be treated with regular prednisolone regimen. If there are two or more relapses in a period of 6 months an alternative therapy should be considered (Abdel-Hafez et al., 2017).

DISCUSSION

First episode of nephrotic syndrome shows the absence of hematuria, hypertension, azotemia. Prednisolone dose is 2 mg/kg/day for 6 weeks followed by 1.5 mg/kg/day alternate days for 6 weeks.

1. Infrequent relapse: Prednisolone 2mg/kg/day until remission, then 1.5mg/kg on alternate days for 4 weeks.
2. Frequent relapse steroid dependance: Alternate day prednisolone to maintain remission, refer for evaluation. Alternate day prednisolone for 9-18 months or given in combination with Levamisole, Cyclophosphamide, Tacrolimus, Mycophenolate mofetil.
3. Steroid resistant: Therapy based on biopsy findings (Thalgahagoda et al., 2017)

Steroid resistant nephrotic syndrome

Failure to achieve remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks is called steroid resistance. Initial resistance: Lack of remission at the first episode. Steroid sensitive initially, but show steroid resistance during subsequent relapse. Most patients show minimal change nephrotic syndrome on renal histology (Kudagammana et al., 2017).

Treatment regimen for steroid resistant nephrotic syndrome

The treatment regimen for steroid resistant nephrotic syndrome is seen in a Table 3. All patients with steroid resistant nephritic syndrome should receive treatment...
with angiotensin converting enzyme inhibitors (enalapril, captopril). These agents should be avoided if the estimated GFR is 30<ml/minute/1.73 m². Angiotensin receptor blockers (Losartan, valsartan) may be used in patients intolerant to ACE inhibitors. Dyslipidemia should be managed with HMG COA inhibitors (Atorvastatin 10-20mg daily). In hypovolaemia conditions add fursomide 1-3mg/kg/day may add spironolactone 2-4mg/kg/day (Abeyagunawardena et al., 2017; Benz et al., 2004).

CONCLUSION

For management of steroid dependent nephrotic syndrome: Prednisolone is gradually tapered to maintain the patient on remission on alternate day dose of 0.5-0.7 mg/kg. A close monitoring on growth, blood pressure and steroid toxicity should be observed. If there is no steroid toxicity with prednisolone 0.5-0.7 mg/kg on alternate days then continue for 9-18 months. If there is any associated steroid toxicity, addition of immunomodulators is suggested. For management of steroid resistant nephrotic syndrome, Immunomodulators along with subsequent administration of steroids should be given. Angiotensin converting enzyme inhibitor drugs along with HMG COA inhibitors are recommended.

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REFERENCES


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