

Case Presentation

Grand Rounds in Pediatric Nephrology

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Received 28 December 2010; Accepted 3 January 2011

Abstract Idiopathic nephrotic syndrome is the most common type of nephrotic syndrome in children and is often associated with life threatening bacterial infections. While the majority of children respond to prednisolone, most have one or more relapses. In children with significant adverse effects of prednisolone, corticosteroid sparing agents may be required. A kidney biopsy is required to guide therapy in those children, whose nephrotic syndrome fails to respond to prednisolone.

Keywords nephrotic syndrome; infection; prednisolone; corticosteroid sparing therapy; kidney biopsy

1 Case presentation

A three-year-old boy is brought to the emergency department because of swelling around his eyes, which has been present for two weeks. In the past 24 hours, the periorbital swelling has become more marked with increasing redness and the child has a fever to 38 degrees Celsius. The child's family doctor had diagnosed conjunctivitis and prescribed some antibiotic eye drops. On examination in the emergency department, the boy is noted to be irritable when examined and to have edema of his legs extending to the thighs with sacral edema and ascites. The cardiovascular and respiratory examinations are within normal limits with no evidence of pleural effusions. The child's weight is 15 kg (50th percentile) while his height is 88 cm (3rd percentile). His blood pressure is 115/70.

2 Questions

- (1) What are the most important two investigations to be carried out immediately?
 - (A) Blood culture and urinalysis for blood and protein.
 - (B) Serum albumin and creatinine, urea and electrolytes.
 - (C) Full blood count and blood culture.
 - (D) Urinalysis for blood and protein and serum albumin.
 - (E) Creatinine, urea and electrolytes and serum cholesterol.
- (2) What is most likely to be the child's diagnosis?
 - (A) Idiopathic nephrotic syndrome.

- (B) Post infectious glomerulonephritis.
 - (C) Idiopathic nephrotic syndrome with periorbital cellulitis.
 - (D) IgA nephropathy.
 - (E) SLE.
- (3) What should be the first treatment given to this child?
 - (A) Intravenous antibiotics.
 - (B) Oral prednisolone.
 - (C) Intravenous albumin with frusemide.
 - (D) Intravenous antibiotics and oral prednisolone.
 - (E) Intravenous methylprednisolone or dexamethasone.
- (4) Assuming that this child has idiopathic nephrotic syndrome, what should the initial prednisolone management regimen be?
 - (A) Daily prednisolone for at least 4 weeks and then cease.
 - (B) Daily prednisolone for at least 4 weeks followed by alternate day prednisolone for at least 8 weeks.
 - (C) Daily prednisolone until the child achieves remission (urine protein on dipstick zero or trace) and cease.
 - (D) Daily prednisolone until the child achieves remission followed by 4 weeks of alternate day prednisolone.
 - (E) Alternate day prednisolone until the child achieves remission.
- (5) Before prednisolone and other corticosteroids were available, most children with nephrotic syndrome died because of bacterial infection. What steps can you take to reduce the risk of severe infection?
 - (A) Ensure that the child has *haemophilus influenzae* type B vaccination.
 - (B) Ensure that the child has vaccination against *Pneumococcus*.
 - (C) Make sure that the family know to seek medical attention when the child is febrile.
 - (D) Teach the family to recognize signs of relapse of nephrotic syndrome.
 - (E) All of the above.
- (6) The child achieves remission after 10 days. What is the chance that this child will have frequent relapses (more than 4 per year) or become steroid dependent (relapse

during prednisolone therapy or within 2 weeks of ceasing prednisolone)?

- (A) 90%.
 - (B) 10%.
 - (C) 40%.
 - (D) 70%.
 - (E) 20%.
- (7) The child relapses 3 months after presentation while receiving alternate day prednisolone. After giving another course of prednisolone to achieve remission, how should this child be treated to maintain remission?
- (A) Cyclophosphamide.
 - (B) Levamisole.
 - (C) Low dose alternate day prednisolone.
 - (D) Low dose daily prednisolone.
 - (E) Diuretics to control edema.
- (8) Over the next two years the child continues to relapse whenever the prednisolone dose is reduced below 0.7 mg/kg on alternate days. While growing well, he has become obese with Cushingoid features and his parents find that he is very aggressive to them and to his siblings. What corticosteroid sparing therapy would you consider first to achieve a prolonged period of remission?
- (A) Cyclophosphamide.
 - (B) Cyclophosphamide or levamisole.
 - (C) A calcineurin inhibitor (cyclosporin or tacrolimus).
 - (D) Levamisole.
 - (E) Mycophenolic acid (mycophenolate mofetil or mycophenolate sodium).
- (9) This boy relapses within 3 months of completing a 12-week course of cyclophosphamide and again while receiving alternate day prednisolone after he has achieved remission with daily prednisolone. What corticosteroid sparing therapy is generally preferred as a second line?
- (A) A calcineurin inhibitor (cyclosporin or tacrolimus).
 - (B) Mycophenolic acid (mycophenolate mofetil or mycophenolate sodium).
 - (C) Levamisole.
 - (D) A second course of cyclophosphamide.
 - (E) Rituximab.
- (10) When would a kidney biopsy be considered essential to guide therapy for a child with idiopathic nephrotic syndrome?
- (A) If he is steroid dependent.
 - (B) Before commencing corticosteroid sparing agents.
 - (C) If he fails to respond to prednisolone initially (initial non-responder) or after one or more remissions with prednisolone (late non-responder).
 - (D) At initial diagnosis of the nephrotic syndrome.
 - (E) To monitor nephrotoxicity during cyclosporin or tacrolimus therapy.

3 Discussion

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia and edema. Massive proteinuria results from structural and functional defects in the glomerular filtration barrier. While the liver tries to compensate with increased albumin production, the loss of urinary albumin exceeds the rate of synthesis, so serum albumin drops and edema develops due to the reduced oncotic pressure. The annual incidence of nephrotic syndrome is around 2 per 100,000 children aged below 15 years in Europe and North America but is higher in the Indian subcontinent and probably in other developing countries.

Nephrotic syndrome in children may be caused by a wide range of disorders, but the most common type in children aged 1–10 years is idiopathic nephrotic syndrome of which about 80% have steroid sensitive nephrotic syndrome (SSNS) with minimal change disease on renal biopsy. Other forms of idiopathic nephrotic syndrome are focal and segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis (MPGN), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulonephritis (MN). There is some evidence that the number of children with FSGS and steroid-resistant nephrotic syndrome is increasing. Infectious agents may cause nephrotic syndrome including hepatitis B (associated with MN), hepatitis C (associated with MPGN), HIV (associated with MPGN, MN, FSGS) and malaria (associated with MN, MPGN). Mutations in genes coding for proteins, including nephrin and podocin in the glomerular filtration barrier, systemic diseases such as SLE and medications (nonsteroidal antiinflammatory agents), are less common causes of nephrotic syndrome.

4 Grand rounds answers

Question (1): (A)

This child requires a urinalysis and blood culture immediately. Bacterial infection usually with *Pneumococcus* or *haemophilus influenzae* is common and serious in untreated nephrotic syndrome in young children, who are dependent on opsonins for splenic processing of these encapsulated organisms. Opsonins and immunoglobulins as well as albumin are lost in the urine of nephrotic children. While the other investigations listed are useful, the results do not usually change the immediate management.

Question (2): (C)

The child is likely to have idiopathic nephrotic syndrome with periorbital cellulitis, though infectious causes of nephrotic syndrome need to be excluded. Although the child has a slightly elevated blood pressure and may have

microscopic hematuria, these are common and transitory in children presenting with idiopathic nephrotic syndrome. Children with post infectious glomerulonephritis have much less edema without ascites but their blood pressure is higher reflecting the fact that the plasma volume is increased due to reduced glomerular filtration rate. In idiopathic nephrotic syndrome, edema occurs because of a reduced oncotic pressure due to low plasma albumin, and plasma volume is usually low. Severe IgA nephropathy presents as an acute nephritic syndrome with hypertension, mild edema and reduced renal function while severe SLE nephropathy will also present as acute nephritis with additional features including rash and arthropathy.

Question (3): (D)

The child should receive intravenous antibiotics (usually penicillin) to treat the child's periorbital cellulitis and also commence oral prednisolone without delay. There are no data to suggest that intravenous methylprednisolone or dexamethasone is superior to oral prednisolone in achieving remission. However, intravenous methylprednisolone might be considered if the child does not tolerate oral medications. Intravenous albumin (1 gm/kg infused over 4 hours) with furosemide (1 mg/kg intravenously after 2 hours of infusion and at the end of the infusion) may be required in very edematous children with gross ascites and scrotal/penile or labial edema. However, these medications should not be used routinely. They can be considered if the renal function is known to be normal and where experienced nursing and/or medical supervision is available as pulmonary edema and death may result.

Question (4): (B)

A systematic review [1] of six randomized controlled trials has shown that the risk of relapse in the initial episode of steroid sensitive nephrotic syndrome (SSNS) is reduced by 30% at 12–24 months if prednisolone is administered for at least three months when compared with two months of prednisolone. An increase in benefit is seen with administration for up to seven months. Daily prednisolone given for one month followed by alternate day prednisolone is more effective than giving prednisolone till remission, followed by alternate day prednisolone. Early observational studies suggested that alternate day prednisolone given at double the dose of daily prednisolone was effective, but this regimen has not been subjected to randomized controlled trials. The usual starting dose of prednisolone is 2 mg/kg or 60 mg/m²/day (given as a single morning dose) for one month followed by alternate day prednisolone for at least two months with a starting dose of 1.5 mg/kg or 40 mg/m² given as a single morning dose on alternate days.

Question (5): (E)

The most likely organisms to cause bacterial infections are *haemophilus influenzae* type b and *Streptococcus pneumoniae* (*pneumococcus*), which generally cause infections (bacteremia, pneumonia, primary peritonitis) when the child is in relapse. Therefore, it is essential that children with nephrotic syndrome receive vaccinations against these organisms. These vaccines can be given when the child is receiving high dose prednisolone. Families should be taught to seek early medical attention when the child is febrile as bacteremia can progress rapidly. The families should also have clear information on the signs of a relapse of nephrotic syndrome and a simple plan of management for a relapse.

Question (6): (C)

Of children presenting with idiopathic nephrotic syndrome, 80–90% will be responsive to prednisolone and are considered to have SSNS. Following remission, about 20% of children do not have further relapses, 40% will relapse infrequently, while the remaining 40% will relapse frequently or be steroid dependent. The risks of a child developing frequent relapses or becoming steroid dependent are increased with shorter time to first relapse, the number of relapses in the first 6 months after initial treatment, younger age at the initial episode, prolonged time to first remission, infection at first relapse and male sex.

Question (7): (C)

It is recommended that in children with steroid-dependent SSNS (SD SSNS), alternate day prednisolone be administered in the lowest dose possible to maintain remission. Following achievement of remission, prednisolone is tapered to 0.5–0.7 mg/kg on alternate days or lower and continued for 9–18 months with careful monitoring for corticosteroid toxicity. Two randomized controlled trials have demonstrated that daily prednisolone dose during upper respiratory tract infection reduced the risk for relapse in children with SD SSNS. Low dose daily prednisolone may be used to maintain remission if alternate day dosing is not effective. It is preferable to try low dose alternate prednisolone before resorting to corticosteroid sparing agents such as cyclophosphamide or levamisole. Because of the risk of infection and the poor quality of life of children in relapse, they should not receive diuretics to control edema without other therapies.

Question (8): (B)

The alkylating agents (cyclophosphamide, chlorambucil), the calcineurin inhibitors (cyclosporin, tacrolimus), levamisole and mycophenolic acid are effective as corticosteroid

sparing agents in frequently relapsing and steroid-dependent SSNS [2]. In randomized controlled trials and observational studies they have been found to increase the duration of remission compared with prednisolone alone. In general, agents are combined with a reducing dose of prednisolone. The choice of the initial agent depends on adverse effects, availability and cost. In general, the initial agent used is either cyclophosphamide or levamisole. Cyclophosphamide is given for 12 weeks at a dose of 2 mg/kg/day and a proportion of children will achieve a prolonged period of remission off all treatment. Though generally well tolerated, cyclophosphamide may cause leucopenia, hair loss, hemorrhagic cystitis, increased risk of bacterial and viral infections and reduced sperm counts. White blood counts should be monitored every two weeks during administration and the dose reduced if the white count falls below $4.0 \text{ cells} \times 10^9/\text{L}$ and not increased again till the white count exceeds $5.0 \times 10^9/\text{L}$. Cyclophosphamide is preferred to chlorambucil since it has a slightly larger window between therapeutic effect and toxicity. In contrast, levamisole is associated with few adverse effects with occasional reports of leucopenia, gastrointestinal disturbance and rarely of cutaneous vasculitis. However, it needs to be continued for 1–2 years since most children will relapse when the medication is ceased. The dose used is 2.5 mg/kg on alternate days.

Question (9): (A)

While levamisole or mycophenolic acid may be given as second line agents in this boy, most pediatric nephrologists find either cyclosporin or tacrolimus to be the most useful agents in children with SD SSNS. However, there are no data from randomized controlled trials to confirm that calcineurin inhibitors (CNI) are more effective than other corticosteroid sparing agents. Cyclosporin is commenced at 5 mg/kg/day in two divided doses while tacrolimus is commenced at 0.1 mg/kg/day in two divided doses. CNIs are associated with nephrotoxicity and hypertension. Tacrolimus is often preferred because, unlike cyclosporin, it does not cause gum hypertrophy and hirsutism. However, it is associated with diabetes mellitus. Mycophenolic acid (MPA) is increasingly being used in children with relapsing SSNS though its relative efficacy to calcineurin inhibitors is uncertain. It is associated with leucopenia, abdominal pain and diarrhoea. CNIs and MPA are continued for 1–2 years and most children relapse when the medications are ceased. Second courses of cyclophosphamide should not be given because of the risk of reduced sperm counts and infertility with a total cumulative dose exceeding 168 mg/kg (equivalent to 2 mg/kg/day for 12 weeks). Rituximab is a monoclonal antibody directed against B cells. Its use should be reserved for children with SD SSNS, who have

continuing frequent relapses despite optimal combinations of prednisone and corticosteroid sparing agents and/or have serious adverse effects of therapy. CNIs, MPA and rituximab are very expensive medications.

Question (10): (C)

A child who fails to respond to 8 weeks of prednisolone is considered to be steroid resistant and should undergo a kidney biopsy to determine the kidney pathology and the extent of glomerular and tubulo-interstitial damage. In populations including African populations where SSNS is less common, some authors recommend that kidney biopsies should be performed at initial diagnosis of nephrotic syndrome. Biopsies should be considered in children receiving CNIs who show deteriorating kidney function particularly if this persists when doses are reduced. Routine biopsies of children with frequent relapsing or SD SSNS before using corticosteroid sparing therapy are not indicated. Studies show that the most important predictor for kidney survival in SSNS is not kidney pathology but the achievement and maintenance of remission with prednisolone and other therapies.

References

- [1] E. M. Hodson, N. S. Willis, and J. C. Craig, *Corticosteroid therapy for nephrotic syndrome in children*, Cochrane Database Syst Rev, 4 (2007), CD001533.
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