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Childhood Nephrotic Syndrome

Developed by Summer Hudson, Dr. Melanie Lewis, and Dr. Catherine Morgan for PedsCases.com.
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Introduction

Hello and welcome to this PedsCases podcast on Childhood Nephrotic Syndrome. My name is Summer Hudson and I am a second year medical student at the University of Alberta. This podcast was developed in collaboration with Dr. Melanie Lewis, a general pediatrician, and Dr. Catherine Morgan, a pediatric nephrologist, who both work at the Stollery Children's Hospital in Edmonton, Alberta, Canada. In this PedsCases podcast we will explore the presentation, diagnosis, and management of Childhood Nephrotic Syndrome. For a detailed review of the evaluation of proteinuria, please review the PedsCases podcast by Peter Gil and Dr. Verna Yiu.

Learning Objectives

By the end of this podcast, listeners will be equipped to:

1. Discuss the clinical presentation and diagnostic criteria for childhood nephrotic syndrome;
2. List key initial investigations to refine the differential diagnosis in children presenting with edema and/or proteinuria;
3. Review an approach for the management of patients with childhood nephrotic syndrome;
4. Recall common complications of childhood nephrotic syndrome; and
5. Delineate outcomes of childhood nephrotic syndrome.

Clinical Case

To learn about the recognition, diagnosis, and management of childhood nephrotic syndrome, let's consider the approach to 6-year-old Lea, who presented to her pediatrician with bilateral

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eye swelling. She is alert and oriented with normal vital signs (including blood pressure). There is a weight gain of 4kg over the 1.5 months since her last appointment.

Key questions reviewed on history include: exploring the evolution of the eye swelling and associated symptoms such as onset of symptoms, eye redness/itchiness/drainage, potential triggers, and remedies tried. You would be considering local causes of eye swelling in addition to systemic illnesses. Local considerations would be infection, allergy and trauma. Systemic illnesses would include any entity that affects fluid dynamics such as: renal, cardiac, liver, and gastrointestinal conditions (the latter two contribute to low protein states). Other specific systemic entities associated with nephrotic syndrome include Hepatitis B, Hepatitis, C, HIV, and SLE. During the review of systems, you would also ask about systemic symptoms such as fatigue, weight change, and fever. To finish, ask about medications, allergies, past medical, surgical, family, and social histories.
Lea's father shares that she has no significant past medical history. She has a known allergy to tree nuts for which she carries an Epi-Pen and has had no subsequent exposures since diagnosis. Lea does not report any itchiness or drainage of the eyes. They attempted Benadryl but the swelling did not change. Upon further interview, Lea's father shares that she has been feeling quite tired and has taken to falling asleep in the car on her way to piano lessons, something she has never done before. This despite sleeping her normal 12 hours every night. When asked about the weight change seen on the growth chart, Lea's father remarks that her clothes no longer fit and Lea herself confirms that she feels uncomfortable and would rather wear her nightgown instead. Given the significant weight gain, you should take a detailed edema history to determine location, duration, severity, and magnitude. You should also investigate for edema on physical exam.
On physical exam, Lea has bilateral periorbital edema with no erythema/itchiness/or drainage, normal oral mucous membranes, clear and symmetric lung sounds with no crackles or wheeze, normal S1 and S2, no murmur, a mildly distended non-tender abdomen, no hepatosplenomegaly, and no masses. You note pitting edema in both legs.
Based on this presentation, Nephrotic Syndrome would likely be the leading diagnosis at this point.
Let's dive into Childhood Nephrotic Syndrome and learn a bit more.

Topic Overview

Epidemiology

Nephrotic Syndrome is one of the most common renal disorders in children, occurring with an international incidence of 2-7 cases per 100,000 and a prevalence of 16 cases per 100,000[1]. It occurs more frequently in boys, with a 2:1 male to female ratio[2]. The median age of onset is 4 years[2].

Normal Physiology

To understand how Nephrotic Syndrome occurs, we must first understand normal glomerular physiology.

The glomerulus is composed of podocytes with foot processes that serve as a barrier to large proteins. As a result, most large proteins, including albumin, remain in the blood and are not filtered into the urine.

Pathophysiology

Nephrotic Syndrome occurs due to podocyte damage in the glomerulus[3]. The result is protein, mostly albumin, leaks out into the urine leading to proteinuria and hypoalbuminemia. The pathophysiology of edema, the clinical hallmark of Nephrotic Syndrome, remains controversial and will not be discussed in this podcast[1].

Nephrotic Syndrome is thus characterized by the triad of proteinuria > 3 g/L (*40 mg/m^2/hour*), hypoalbuminemia < 25 g/L, and edema[2,4]. All three of these features are necessary for diagnosis. In addition to this triad, patients with Nephrotic Syndrome experience hyperlipidemia as the liver increases lipoprotein synthesis as a reaction to low plasma oncotic pressure[1]. Note that hyperlipidemia is NOT necessary to confirm the diagnosis of Nephrotic Syndrome[2].

Presentation

So how does nephrotic syndrome typically present?

As in Lea's case, children with Nephrotic Syndrome often present with bilateral periorbital edema that is initially misdiagnosed as an allergic reaction[2]. Edema becomes detectable when fluid retention reaches 3-5% of body weight[5]. Edema is also commonly seen in the face, abdomen, sacrum, lower limbs, and in severe cases, in the scrotum or labia[2]. On physical exam, be sure to look for the indentation of sock cuffs on the legs as a marker of lower limb edema. Other associated clinical features may include fatigue and poor appetite, both attributable to ascites, as well as weight gain incompatible with the child's growth chart due to edema[5]. Nephrotic Syndrome is rarely identified incidentally on routine urinalysis[6].

Diagnosis

Upon suspicion of Nephrotic Syndrome, urinalysis and serum albumin measurement should be performed. Nephrotic Syndrome in children can be diagnosed in the presence of edema, proteinuria > 3 g/L (*40 mg/m^2/hour, 50 mg/kg/d*), and hypoalbuminemia < 25 g/L [2]. Note that the urine dipstick test measures protein concentration, not the rate of protein excretion, and as such cannot be used to diagnose Nephrotic Syndrome[3]. However, it can be used as a screening test, with most children with Nephrotic Syndrome yielding >= 3+ proteinuria[3]. Initial investigations should include: urinalysis, urine protein/creatinine ratio, electrolytes, urea,

creatinine, glucose, cholesterol, serum albumin, serum lipids, C3/C4, Hepatitis B, Hepatitis C, and HIV serology, anti-nuclear antibody, and anti-dsDNA[7].

Etiology

Idiopathic Minimal Change Disease, caused by the diffuse effacement of podocyte foot processes, is the underlying cause of Nephrotic Syndrome in 70-90% of children[6]. As such, a presumptive diagnosis of Minimal Change Disease can be made if the patient is younger than 10 years, does not have hypertension, does not have hematuria, has normal complement levels, and has normal renal function[8]. Several features suggest an etiology other than Minimal Change Disease, warranting further investigation. These include age younger than 1 year, extrarenal disease such as rash/arthritis/anemia, hypertension, pulmonary edema, renal failure, hematuria, and red blood cell casts in the urine[1]. Other more rare causes of Childhood Nephrotic Syndrome include Focal Segmental Glomerulosclerosis and Membranous Nephropathy[5]. Moving forward, this podcast will focus on Nephrotic Syndrome caused by idiopathic Minimal Change Disease, as this is the most common etiology seen in pediatrics.

Let's get back to our case. Lea's lab results are back, and her urine protein is measured at 4.4 g/L. This is considered to be in the nephrotic range. Her albumin is measured to be 10 g/L. These results, in addition to her edema, confirm the diagnosis of Nephrotic Syndrome. Lea's age, lack of hypertension, and lack of hematuria suggest idiopathic Minimal Change Disease as the cause.

Management

What should be done to help Lea?

95% of children with Nephrotic Syndrome are steroid-sensitive and will achieve remission following a 12-week course of oral Prednisone therapy (2 mg/kg/d (maximum 60 mg/m^2) for 6 weeks followed by 1.5 mg/kg/d (maximum 40 mg/m^2) for 6 weeks)[1,7]. Initial response is usually rapid, with 75% of children remitting after only 2 weeks of treatment[1]. As a result, kidney biopsy is not recommended for patients who respond to steroid treatment[2]. Note that if the child does not respond to steroid therapy, further investigation should be undertaken to investigate for an alternate etiology. There is a high relapse rate, which can be alleviated by lengthened corticosteroid regimens, though most children outgrow the disease and cease to experience relapses past age 18[1,2]. It should be noted that lengthened corticosteroid regimens amplify the unfortunate side-effects in many patients, so family counselling is imperative to help navigate these[2]. Side effects include swelling of the face and extremities, increased appetite and weight gain, acne and hirsutism, and mood changes, among others[2].

For children who are unresponsive to initial treatment with Prednisone, alkylating agents, calcineurin inhibitors, and high-dose pulse methylprednisone may be attempted[1].

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Monitoring
After initial treatment, children with Nephrotic Syndrome should be monitored closely over the first year to monitor for progress, complications, and side effects of corticosteroid therapy[2].

Complications & Side Effects
We will now discuss each of the common complications and recommendations for managing them.

Edema is a very common and distressing complication for children to experience and parents to witness. Severe edema can cause difficulty breathing (due to pleural effusion), abdominal pain (due to ascites), skin breakdown, difficulty walking, and scrotal or labial edema[2,3,5]. To address edema, the child should be placed on a fluid and sodium restricted diet. Sodium restriction has the benefit of reducing thirst, thereby facilitating fluid restriction. Specific intake recommendations depend on both weight and gender, so a reference table should be consulted before making any orders or recommendations to the family. The Department of Pediatric Nephrology at BC Children's Hospital recommends this general rule of thumb: children with Nephrotic Syndrome should be limited to 1mg of sodium for each calorie they consume while on Prednisone[2]. As a rule, the child should ingest no added salt[5]. BC Children's also recommends restricting total fluid intake to 50% of normal maintenance requirements until remission is achieved, at which point fluid limitation can be stopped[2].

Cases of severe edema, or anasarca, may warrant intravenous albumin and furosemide therapy to alleviate the volume contracted state[2,5]. Note that referral to a pediatric nephrologist is critical if this is the case.

Infections are also very common among children with nephrotic syndrome, as these patients are immunocompromised due to Prednisone therapy as well as impaired T-lymphocyte function and loss of IgG and complement in the urine[1,2]. To mitigate risk for severe infections, strict handwashing, avoidance of sick contacts, and up-to-date immunization are crucial. Note that live vaccines cannot be given to those actively nephrotic or those who have undergone high-dose Prednisone therapy (i.e. >60 mg/m^2 or >20 mg/day) for at least 14 days in the past month[2]. Furthermore, all family members should be immunized, if possible, to minimize risk to children with Nephrotic Syndrome with incomplete immunization[2]. Given the severity of influenza and pneumococcal infections in children with Nephrotic Syndrome, all patients should be immunized at initial presentation regardless of nephrotic or Prednisone status[2,5].

Children with Nephrotic Syndrome are also at elevated risk for venous and pulmonary thromboemboli due to urinary loss of protective proteins such as antithrombin III and prolonged immobilization due to edema[1,2]. Most events occur early in the disease course with use of central lines and in those patients older than 12 years with previous history of

thromboembolism[2]. Prophylactic anticoagulation carries risks and is only recommended in high risk patients and in consultation with a pediatric nephrologist[1,2].

Prednisone therapy also confers risk of developing cataracts and glaucoma[2]. As such, all children with Nephrotic Syndrome should see a pediatric ophthalmologist at 4 weeks post-diagnosis, when Prednisone exposure is at its maximum[2].

Another complication of Prednisone therapy is diminished bone mass, which confers risk of fractures, bone pain, and decreased growth. To ameliorate this, children with Nephrotic Syndrome should be prophylactically initiated on daily supplemental calcium and vitamin D at doses of 500 mg and 800-1000 IU, respectively[2,5].

The last main complication to look out for is hyponatremia, that is, a serum sodium <135 nmol/L. This often occurs at initial presentation and during relapses due to elevated antidiuretic hormone release. Hyponatremia can usually be reversed with IV albumin, so this is recommended in place of IV sodium or hypertonic saline which should not be used[2]. As always, consultation with a pediatric nephrologist is encouraged.

Prognosis

Now that we have learned how to diagnose and manage Nephrotic Syndrome and its complications, let's discuss the prognosis and outcomes for children with this condition.

As previously mentioned, most children with Nephrotic Syndrome are responsive to treatment with steroids and will remit within 4 weeks of prednisone treatment and almost all will remit by 6 weeks[2]. 60-80% of children who are steroid-sensitive will relapse with roughly 60% of those children experiencing greater than 5 relapses[1]. After the first year of remission, most cases can be monitored successfully with at-home urine dipstick testing to measure urine protein content[2]. Children and parents often become adept in this at-home monitoring, along with visually inspecting the urine for a foamy appearance as a marker of proteinuria[5].

Conclusion

Let's review some take-home points on Childhood Nephrotic Syndrome.

1. Criteria for the diagnosis of Childhood Nephrotic Syndrome:
    - Proteinuria > 3 g/L
    - Hypoalbuminemia < 25 g/L
    - Edema
2. Review the most common cause of Childhood Nephrotic Syndrome: Minimal Change Disease.

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3. Review common clinical presentations of Childhood Nephrotic Syndrome: bilateral periorbital edema, facial, sacral, lower limb, and scrotal or labial edema. Fatigue, poor appetite, and weight gain are other common associated findings.
4. Review the essential tenets of treating Childhood Nephrotic Syndrome:
    - Oral Prednisone at a dose of 2 mg/kg/d for 12 weeks
    - Sodium and fluid restricted diet
    - Pneumococcal and influenza vaccination at first presentation as well as familial immunization if possible
    - Supplemental 500mg calcium and 800-1000 IU vitamin D daily to promote bone density

Overall, we have discussed edema as a common presentation of Childhood Nephrotic Syndrome along with other associated clinical findings. The management of Childhood Nephrotic Syndrome caused by Minimal Change Disease should consist of Prednisone treatment, complication management, and consistent monitoring to ensure progress towards and maintenance of remission. As always, refer to your local institutional practice points for specific guidance. Thank you for joining us on this episode of PedsCases and stay tuned for more interesting and educational content!

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