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FACTORS PREDICTIVE OF REMISSION IN STEROID SENSITIVE NEPHROTIC SYNDROME OF PAEDS -A Review

Syeda Javaria Nadir [1], Nazish Saleem[1], Fatima Amin[1], Khawaja Tahir Mahmood[2]

[1]Department of Pharmacy, Lahore College for Women University, Lahore, Pakistan
[2]DTL, Lahore,Pakistan.

ABSTRACT

Nephrotic syndrome (NS) is the commonest glomerular disorder in childhood. It is a chronic distressing disorder characterized by heavy proteinuria, hypoproteinaemia, edema and Hyperlipidemia. Nephrotic syndrome is a set of signs or symptoms that may point to kidney problems, a condition when large amounts of protein leak out into the urine. In children protein excretion of more than 40 mg/m^2/hr. indicate presence of nephrotic syndrome. Edema is the predominant feature of nephrotic syndrome and initially develops around the eyes and legs. Despite the occurrence of relapses, steroid sensitive nephrotic syndrome (SSNS) has a good long term prognosis. As it often heralds a clinical relapse, significant proteinuria (+++ or more on albustix) for [greater than or equal to] 3 consecutive days (simplified as P3D in this letter) defines a relapse, resulting in steroid therapy before the onset of edema. The 1st line treatment given is steroid therapy in the pre-antibiotic era children with NS often died, usually from overwhelming infections arising as a result of the immunosuppression which is an inherent feature of the disease and, poor nutrition. The importance of the immune system in the pathogenesis of childhood NS was first suggested in 1974. However, even many decades before this, it was known that after an attack of measles, NS could enter long term remission. But Corticosteroids have reduced the mortality rate to around 3%. The review paper describes interesting findings which have been observed , recorded and reported on this subject.

Key Words: *Relapse, Remission, Steroid Sensitive Nephrotic syndrome (SSNS), Steroid resistance.*

INTRODUCTION

Nephrotic syndrome is a collection of symptoms which occur because the tiny blood vessels (the glomeruli) in the kidney become leaky. This allows protein (normally never passed out in the urine) to leave the body in large amounts. Nephrotic range proteinuria is present if early morning urine protein is 3+/4+ (on dipstick or boiling test), spot protein/creatinine ratio >2 mg/mg, or urine albumin excretion >40 mg/m ^{2} per hour (on a timed-sample). Precise quantitative assessment of proteinuria, including 24-h urine protein measurement is seldom necessary. [1, 2] Prednisolone was used for children with nephrotic syndrome in 1956, four children (age 2-8 years) all of whom responded to prednisolone 60 mg daily. [3]. Subsequently a dosage of 60 mg/m^2/day has been accepted as standard treatment. There have been several studies that have looked at the effect of duration of prednisolone in relation to long term outcomes. The dose of prednisolone required to achieve remission has not been studied. Today most children with initial onset of NS beyond the first year of life will be treated with corticosteroids without an initial biopsy. [4] In the pre-antibiotic era children with NS often died, usually from overwhelming infections arising as a result of the immunosuppression which is an inherent feature of the disease and, poor nutrition. The importance of the immune system in the pathogenesis of childhood NS was first suggested by Shalhoub in 1974. With the introduction of corticosteroid therapy for treatment of childhood NS, the mortality has dropped from 35 to 3%.

Dose:-Standard regime as first line therapy is prednisolone -60 mg/m2/day in 3 divided doses for 4 weeks followed by 40 mg/m2/day in a single dose on every alternate day for 4 weeks [6].

Relapse: It is most common chronic renal disease of childhood and the most common type of idiopathic, among whom about 84.5% have minimal change lesion in kidneys. Most children achieve a complete remission when treated with oral prednisolone, however, even most responsive patient are likely to relapse. But some children have complicated patterns of response. [7]

Despite the occurrence of relapses, steroid sensitive nephrotic syndrome (SSNS) has a good long term prognosis. As it often heralds a clinical relapse, significant proteinuria (+++ or more on albustix) for ≥3 consecutive days (simplified as P3D in this letter) defines a relapse, resulting in steroid therapy before the onset of oedema. Proteinuria may be triggered by viral infections and does not always develop into a relapse [8]

DEFINITIONS RELATED TO NEPHROTIC SYNDROME [9]

Remission Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens.

Relapse Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, having been in remission previously.

Frequent relapses Two or more relapses in initial six months or more than three relapses in any twelve months.

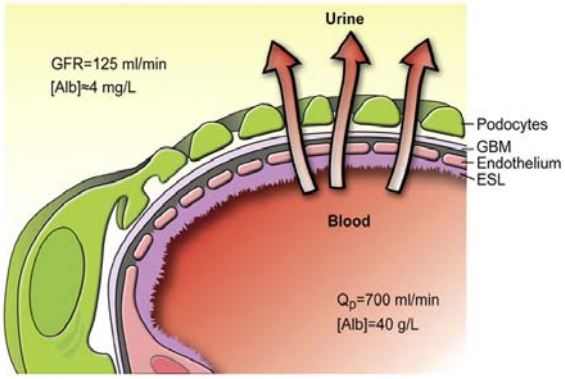
Steroid dependence Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation

Steroid resistance Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks.

PATHOPHYSIOLOGY

Glomerular permeability:-

The glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes. In between the foot processes are the filtration slits. These 3 structures the fenestrated endothelium, glomerular basement membrane, and glomerular epithelium are the glomerular filtration barrier. A schematic drawing of the glomerular barrier is seen in the image below.



Schematic drawing of the glomerular barrier. Podo = podocytes; GBM = glomerular basement membrane; Endo = fenestrated endothelial cells; ESL = endothelial cell surface layer (often referred to as the glycocalyx). Primary urine is formed through the filtration of plasma fluid across the glomerular barrier (arrows); in humans, the glomerular filtration rate (GFR) is 125 mL/min. The plasma flow rate (Q_p) is close to 700 mL/min, with the filtration fraction being 20%. The concentration of albumin in serum is 40 g/L, while the estimated concentration of albumin in primary urine is 4 mg/L, or 0.1% of its concentration in plasma. [10]

Pathogenesis of edema:-

Capillary hydrostatic pressure and the gradient of plasma to interstitial fluid oncotic pressure determine the movement of fluid from the vascular compartment to the interstitium. The oncotic pressure is mainly determined by the protein content. The flux of water across the capillary wall can be expressed by the following formula:

$$\mathbf{Q_w = K ([P_c - P_i] - [p_p - p_i])}$$

In this formula, Q_w is net flux of water, K is the capillary filtration coefficient, P_c is capillary hydrostatic pressure, and P_i is the interstitial fluid hydrostatic pressure, while p_p is the plasma oncotic pressure, and p_i is the interstitial fluid oncotic pressure. [11]

CLASSIFICATION:-

Nephrotic syndrome can be primary; being a disease specific to the kidneys, or it can be secondary, being a renal manifestation of a systemic general illness. In all cases, injury to glomeruli is an essential feature. [12]

From a therapeutic perspective, nephrotic syndrome may be classified as steroid sensitive, steroid resistant, steroid dependent, or frequently relapsing. [13]

DIAGNOSIS

Urine analysis:-

To diagnose childhood nephrotic syndrome, the doctor may ask for a urine sample to check for protein. The doctor will dip a strip of chemically treated paper into the urine sample. Too much protein in the urine will make the paper change color. Or the doctor may ask for a 24-hour collection of urine for a more precise measurement of the protein and other substances in the urine. [14]

A strip of chemically treated paper will change color when dipped in urine with too much protein. [15]

Blood sampling:-

The doctor may take a blood sample to see how well the kidneys are removing wastes. The level of albumin in the blood is low because this vital protein is excreted in the urine and its production is impaired. Healthy kidneys remove creatinine and urea nitrogen from the blood. If the blood contains high levels of these waste products, some kidney damage may have already occurred. But most children with nephrotic syndrome do not have permanent kidney damage. [16].

Biopsy:-

In some cases, the doctor may want to examine a small piece of kidney tissue with a microscope to see if something specific is causing the syndrome. The procedure of collecting a small tissue sample from the kidney is called a biopsy, and it is usually performed with a long needle passed through the skin. [17]

FACTORS LEADING TO RELAPSE

Who gets it?

In most cases there is no known cause of nephrotic syndrome but research is beginning to provide us with more information about the actual changes in the kidney.

Childhood nephrotic syndrome is an uncommon condition. Every year approximately two to seven children in every 100,000 develop nephrotic syndrome. It tends to be more common in the Arab and Asian populations and in families with a history of allergies. Nephrotic syndrome often starts between the ages of two to five years, affecting twice as many boys as girls. [18]

In children, there are four major causes of the NS. The most common and the one with the best outcome are called Minimal Change Nephrotic Syndrome (MCNS). All told, about 80% of children with nephrosis will have this diagnosis. Other relatively common types of nephrosis are Focal Segmental Glomerulosclerosis (FSGS), Membrano proliferative Glomerulo nephritis (MPGN), or Membranous glomerulopathy (Membranous). A very small number of children will have other diagnoses. [19]

What causes it?

That's a tough question and for the most part, we still don't know the answer. For just a few patients, it seems clear that NS is related to a chronic infection or is caused when the body tries to get rid of an invading protein (an immune reaction). However, in most children, we still don't know why nephrosis develops. Whatever the underlying cause, it looks as if the kidney's filtering system develops bigger holes and starts allowing some parts of the blood (such as protein and red blood cells) to be filtered, and therefore lost into the urine. [19]

What causes the swelling and weight gain?

Holding on to extra salt

we have already explained that the swelling we see in children with the NS is caused by water seeping out of the blood vessels into other body tissues. That explains why water shifts places within the body, but not why the total amount of water increases. The main reason is that in addition to water shifting, there are other changes that make the body want to hold on to extra salt. Whenever you hold onto extra salt you also hold onto water. Patients with the NS hold onto salt very strongly. For every teaspoon of salt that is retained, over two pounds of water are also retained, so weight increases and your child looks swollen. [19]

Prednisolone treatment

Prednisolone also causes salt retention as well as a big increase in appetite. The final result is that patients with the NS both retain salt and water and eat more, gaining fat as well as water. [19]

What causes a relapse?

Just as we don't know why children develop nephrosis, we don't really understand why the NS returns. Experience, however has allowed us to make some general comments. [19]

Fever or infection

we know that fever or infection will increase urinary protein levels in all of us. Children with nephrosis are just as likely to have other illnesses as children without nephrosis and their urinary protein levels may also increase. Unfortunately, for some of these children, once their urine protein levels begin to rise, they continue to go up even when the infection is over. In these children we have to restart or increase the amount of prednisone to get them back into remission. We will often try and hold off as long as we can before restarting prednisone. You can help by remembering how your child responds to a fever; by remembering his regular weight (so we can tell if he has gained weight) and by checking the morning urine for protein at the first sign of illness. [19]

Lowering the dose of prednisone

Each child is different and may respond in different ways as we lower the prednisone. We try to lower the dosage of prednisone as fast as we can to minimize side effects while going slowly enough to prevent a relapse. You will become very knowledgeable about your own child's response, and we will ask for your help and memory as we work with you to treat your child. [19]

Allergies

For just a few children, the NS can be triggered by an allergy. This is not common but has been noted in the literature. [19]

MANAGEMENT

General Measures:-

Diet

In the past, both low and high protein diets have been recommended for SSNS. A low protein diet reduces albuminuria but increases the risk of malnutrition. Animal studies show that high protein diets increase the synthesis of albumin, but do not increase the albumin concentration or growth significantly. Based on current evidence, no specific dietary advice is necessary for uncomplicated cases of SSNS. Modest salt restriction is beneficial during severe relapses, especially in patients with edema. [14]

Activity

All efforts should be taken to actively mobilize the child; bed rest should be avoided if possible to minimize the risk of thrombosis. [15]

Immunizations

All killed vaccines are generally regarded as safe for administration when a child is in remission. All live vaccinations should be avoided until children are off daily steroids for at least 6 weeks. [16]

SPECIFIC THERAPY

Induction of Remission

Corticosteroids

Corticosteroids remain the drug of first choice for induction of remission. While there are no controlled trials that have compared the efficacy of prednisone with prednisolone, both medications are comparable. The treatment protocol, prednisolone 60 mg/m2 daily in divided doses for 4 weeks followed by 40 mg/m2 / day prednisolone for 3 consecutive days of a week (intermittent) for the next 4 weeks, designed by ISKDC over 35 years ago was empirical. However, current practice is to prescribe alternate day therapy in the second month of treatment in preference to intermittent therapy because it reduces the relapse rate more effectively. [17]

MECAHNISM OF ACTION:-Prednisone is a glucocorticoid agonist. It is first metabolized in the liver to its active form, prednisolone. Prednisolone crosses cell membranes and binds with high affinity to specific cytoplasmic receptors. The result includes inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune

responses, and reduction in edema or scar tissue. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. [18]

Side Effects:-

Possible side effects include fluid retention of the face, acne, constipation, and swings. A lengthy course of prednisolone can cause bloody or black tarry stools; filling or rounding out of the face; muscle cramps or pain; muscle weakness; nausea; pain in back, hips, ribs, arms, shoulders, or legs; reddish-purple stretch marks on arms, face, legs, trunk or groin; thin and shiny skin; unusual bruising; urinating at night; rapid weight gain; and wounds that will not heal. Swelling of the pancreas has also been reported. Other effects include decreased or blurred vision, increased eye pressure, increased thirst, confusion, rare cases of dementia. It also is reported to cause insomnia when taken. [19]

CONCLUSION

Nephrotic Syndrome is not exclusively a disease of the poor, deprivation associated with poverty increases the risks of infection and development of disease. There are clear associations between risk of Nephrotic Syndrome and malnutrition, illetracy, unawareness, overcrowding and negligence. Recognizing Nephrotic Syndrome as a social, economic and political disease, and not just a medical problem, prompts the need to explore new avenues through which efforts to ensure Nephrotic Syndrome prevention and access to its cure is to be strengthened. In the light of above study it was concluded that Nephrotic syndrome is rationally treated by Steroidal therapy but the recurrence of Nephrotic syndrome is also commonly seen because the course of treatment of Steroid therapy is prolonged and people usually skip the dose of the drug due to negligence towards the therapy. Normally 3-4 tablets TID are given which frustrate them to take so many tablets at a time which results in relapse. The protocol of steroid therapy in case of associated diseases is carefully followed, as in case of T.B. the immunity is depressed so steroids are not taken alone, they are then taken in combination with immuno stimulants like Levamisole.

Many factors may cause the relapse of primary nephrotic syndrome, including too short steroid treatment period, rapid tapering off the dose of prednisone, infections, etc. The most important factor is too short prednisone treatment period.

Children with nephrotic syndrome may have trouble regulating their body's water balance. This can cause fluid retention (also known as edema). The diet for a child with nephrotic syndrome may include a sodium and fluid restriction. These restrictions in the diet may help to regulate your child's fluid balance.

RECOMMENDATIONS

The identification of paeds at high risk and an accurate management of their therapy are the important challenges for health care professionals to avoid serious consequences caused by Nephrotic Syndrome. Consider the following recommendations, which, if followed, are highly effective in treating Nephrotic Syndrome.

- Illetracy, unawareness, negligence, unhygienic conditions and malnutrition are the major causes of many diseases including Nephrotic syndrome in our Country. For this purpose State and local health Department should establish a comprehensive informational and investigational Programme to ensure that rational therapy should be followed.
- Seminars should be conducted for the awareness of the disease, its hazards and how the disease can be prevented.
- The course of Steroidal therapy should be completely done to avoid recurrence of the disease.
- No self-medication should be taken before the confirmation of the right disease.
- To avoid edema, excessive salt and water intake should be minimized.
- A child should not do heavy exercise and physical exertion as proper rest is required

to avoid exhaustion.

- Immunostimulants (levamisole) should be given in combination with steroid, if a child has some immunodepressant associated disorder (like T.B)
- Therapy needs to be individualized for each patient and optimal care will be achieved by combined inputs of the primary pediatrician and pediatric nephrologist.
- Guidelines regarding the initial evaluation, indications for renal biopsy and referral to a pediatric nephrologist must be updated.
- It is proposed that patients with frequently relapsing nephrotic syndrome should, at the first instance, be treated with long-term, alternate-day prednisolone.
- The principles of dietary therapy, management of edema, and prevention and management of complications related to nephrotic syndrome should be described.

The pharmacist should counsel the patient properly about continuing and completing the whole therapy.

REFERENCES

[1]. Arneil GC (1971) The nephrotic syndrome. Pediatr Clin North Am 18:547–559

[2]. Arbeitsgemeinschaft f_r P_diatrische Nephrologie (1988) Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Lancet 1:380–383

[3]. Arneil GC. Treatment of nephrosis with prednisolone. Lancet 1956;i:409-11.

[4]. Spirer Z, Hauser GJ. Corticosteroid therapy in pediatric practice. Adv Pediatr 1985;32:549-87. Correspondence to Dr I A Choonara, Division of Clinical Pharmacology, University Hospital, S-751 85 Uppsala, Sweden.

[5]. Hodson E, Willis N, Craig J (2007) "Corticosteroid therapy for nephrotic syndrome in children". Cochrane database of systematic reviews (Online)

[6]. Stanely A, Mendoza and Bruce M. Management oF difficult nephrotic patient. Paediatric Clin N Am 1995; 42(6): 101

[7]. Arch Dis Child 2004;89:395 doi:10.1136/adc.2003.033889

[8]. Haraldsson et al, Physiol Rev 88: 451-487, 2008

[9]. Hamm LL, Batuman V. Edema in the nephrotic syndrome: new aspect of an old enigma. *J Am Soc Nephrol*. Dec 2003; 14(12):3288-9

[10]. Zukerman E, Ingelfinger JR. Coping With Prednisone. New York, NY: St Martin's Press; 1997

[11]. Bagga A, Srivastava RN. Nephrotic syndrome. In: Srivastava RN, Bagga A, editors. *Pediatric Nephrology*. 4th ed. New *Delhi: Jaypee; 2005 p. 159-200.)*

[12]. Tune BM, Mendoza SA. Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. J Am Soc Nephrol 1997;8:824–32.

[13]. Madaio MP, Harrington JT. The diagnosis of glomerular diseases: acute glomerulonephritis and the nephrotic syndrome. Arch Intern Med 2001;161:25–34

[14]. Roberts WL, Calcote CB, Cook CB, et al. Comparison of four commercial urinary albumin (microalbumin) methods: implications for detecting diabetic nephropathy using random urine specimens. Clin Chim Acta 1998;273:

[15]. Guideline] International Study of Kidney Disease in Children (ISKDC). Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. Feb 1978;13(2):159-65

[16]. Guideline] International Study of Kidney Disease in Children (ISKDC). The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr. Apr 1981;98(4):561-4.

[17]. Mendoza SA, Tune BM. Treatment of childhood nephrotic syndrome. J Am Soc Nephrol1992; 3: 889–894

[18]. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol. Mar 2001;16(3):271-82

[19]. Penn State Milton S. Hershey Medical Center ©2004 October 31, 2006

[20]. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft für Pädiatrische Nephrologie. Eur J Pediatr. Apr 1993;152(4):357-61

[21]. Sinha MD, MacLeod R, Rigby E, Clark AG. Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. Nephrol Dial Transplant. Jul 2006;21

[22]. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev. 2007;(4):CD001533.

[23]. Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. N Engl J Med. Mar 30 2006;354(13):1387-401

[24]. Takeda A, Takimoto H, Mizusawa Y, Simoda M (2001) Prediction of subsequent relapse in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol 16:888–893