DEMOGRAPHIC PROFILE OF CHILDREN WITH NEPHROTIC SYNDROME IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By

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ABBREVIATION

ACE	Angiotensin Converting Enzyme
CAPD	Continuous Ambulatory Peritoneal Drainage
FBC	Full Blood Count
FSGS	Focal Segmental Glomerular Sclerosis
HUSM	Hospital Universiti Sains Malaysia
INS	Idiopathic Nephrotic Syndrome
ISKDC	International Study of Kidney Disease in Children
IQR	Interquarter Range
LFT	Liver Function Test
MC	Minimal Change
MCNS	Minimal Change Nephrotic Syndrome
MGN	Membranous Glomerulonephritis
MPGN	Membranoproliferative Glomerulonephritis
NS	Nephrotic Syndrome
RF	Renal Failure
RFT	Renal Function Test
SDNS	Steroid Dependent Nephrotic Syndrome
SRNS	Steroid Resistant Nephrotic Syndrome
SSNS	Steroid Sensitive Nephrotic Syndrome
UFEME	Urine Full Examination Microscopic Examination
VZIG	Varicella Zoster Immunoglobulin

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ABSTRAK

Penyakit sindrom nefrotik adalah penyakit yang berkaitan dengan masalah buah pinggang. Penyakit ini boleh dikesan apabila terdapat tanda-tanda seperti kekurangan albumin di dalam darah, pengeluaran protin di dalam air kencing yang banyak atau tidak normal dan edema. Penyakit ini kerap berlaku di kalangan kanak-kanak yang berumur di antara 1 hingga 6 tahun. Penyakit sindrom nefrotik ini biasanya dirawat dengan ubat 'steroid' dan hampir 70% daripada pesakit akan mengalami ulangan atau 'relapse' dan bergantung kepada ubat 'steroid' Terdapat juga kes-kes di mana tiada tindakbalas terhadap ubat steroid. Bagi kes-kes tersebut ubat 'immunosuppressive' seperti 'cyclosporine A, cyclophosphamide, chlorambucil dan levamisole' akan digunakan.

Tujuan Kajian

Kajian ini adalah untuk melihat faktor-faktor demografik bagi kanak-kanak sindrom nefrotik yang di rawat di Hospital Universiti Sains Malaysia. Di samping itu juga untuk mengkaji kesan sampingan dan fungsi buah pinggang yang wujud akibat dari pengambilan ubat 'cyclosporine'.

Metodologi

Kajian retrospektif di mana semua kanak-kanak sindrom nefrotik yang berusia 15 tahun ke bawah akan dikaji. Analisa data akan dilakukan dengan program 'Statistical Package for the Social Sciences Programmed (SPSS)' versi 12.0. Untuk setiap kes pembentangan keputusan kajian diterjemahkan dalam bentuk peratusan, median dan 'interquarter range'. Manakala perbezaan antara pemboleh-ubah selanjar dilakukan dengan 'Friedman test'. Kebarangkalian statistik diterjemahkan dengan nilai $p<0.05$

Keputusan

Terdapat 83 orang kanak-kanak sindrom nefrotik yang di rawat di HUSM (Hospital Universiti Sains Malaysia) dan merupakan 0.48% dari kes yang dimasukkan ke wad kanak-kanak di HUSM semasa kajian dijalankan. Kebanyakan pesakit adalah berketurunan Melayu 98.8% (n=82) dan 79.5% (n=66) adalah dari negeri Kelantan. Ubat cyclosporine digunakan didalam 21.6% (n=18) kes sindrom nefrotik yang dirawat di HUSM. Didapati 66.7% (n=12) dari penggunaannya adalah disebabkan oleh rintangan terhadap ubat steroid dan 33.3% (n=6) akibat kesan sampingan ubat steroid. Kesan sampingan yang terjadi akibat dari pengambilan ubat ini adalah bengkak gusi 55.6% (n=10), 'hirsutism' 16.7% dan kerosakkan buah pinggang 16.7% (n=3). Darah tinggi berlaku di dalam 14 pesakit sebelum rawatan dengan ubat 'cyclosporine' dan 12 orang masih mengalami darah tinggi selepas rawatan, manakala 2 orang tidak diketahui kerana tidak ada rawatan susulan. Empat orang pesakit tidak mengalami darah tinggi sama ada sebelum atau selepas rawatan. Sebanyak 57.0% dan 60.0% dari kumpulan rintang terhadap ubat steroid dan kumpulan yang mengalami kesan sampingan ubat steroid mempunyai fungsi buah pinggang yang normal selepas 5 tahun.

Kesimpulan

Kebanyakan kanak-kanak sindrom nefrotik yang dirawat di Hospital Universiti Sains Malaysia adalah dari kumpulan yang sensitif terhadap ubat steroid. Penggunaan ubat 'cyclosporine' adalah selamat dan ia digunakan bagi kanak-kanak sindrom nefrotik yang mengalami rintangan terhadap ubat steroid dan yang mengalami kesan sampingan terhadap ubat steroid.

ABSTRACT

Steroid is still the mainstay therapy for nephrotic syndrome and up to 70% of children had frequent relapses or steroid dependent. But some of the cases are resistant to steroid therapy. Immunosuppressive drugs, such as cyclosporine A, cyclophosphamide, chlorambucil and levamisole have proved effective as steroid-sparing agents. Cyclosporine was first started in our hospital HUSM (Hospital Universiti Sains Malaysia) in 1996 for steroid resistant NS (nephrotic syndrome) following renal biopsy. There were no published data from locally regarding the demographic profile of the children with nephrotic syndrome, the outcome, side effect and prognosis toward development of renal failure in children with NS treated with cyclosporine.

Objectives: To describe the demographic data of children with nephrotic syndrome treated in HUSM. To determine common side effect that are related to the use of cyclosporine and development of renal failure in children with nephrotic syndrome treated with cyclosporine.

Methodology: This is a retrospective study in which all children with NS below 15 years old were reviewed. All the results were analyzed using Statistical Package for the Social Sciences Programmed (SPSS) for Window version 12.0. For each case, demographic data, renal biopsy results, respond and side effect were presented by percentage, median and interquarter range. Friedman test were used to assess differences between repeated continuous variables. Statistical significance was inferred at $p < 0.05$.

Result: There were 83 children's with nephrotic syndrome on treatment and follow up at HUSM. These figures give about 0.48% of the total admission of paediatric medical cases to HUSM during study period. The mean age at presentation was 6.39 (±SD3.41) years.

Children with steroid sensitive nephrotic syndrome occurred in 85.5% (n=71) compare to children with steroid resistant nephrotic syndrome occurred in 14.5% (n=12). Relapse occurred in 63.9% of all NS children (n=53) and 36.1% of children (n=30) had no relapse. There were 57.7% of children (n=41) with SSNS (steroid sensitive nephrotic syndrome) experience relapse and 42.3% of these group of children (n=30) had no relapse. Cyclosporine has been used in 21.6% [95%CI (12.6%, 30.7%)] of NS children (n=18) and 66.7% (n=12) of the children were due to steroid resistant and 33.3% (n=6) of the children were due to steroid toxicity. Side effects noted in this study were gum hypertrophy 55.6% (n=10), hirsutism 16.7% (n=3) and renal impairment 16.7% (n=3). There were 27.8% (n=5) of these children, free of any side effects. There were 14 out of 18 children had hypertension before cyclosporine and 12 of them still noted to have hypertension after cyclosporine, 2 children loss follow up and 4 children had no hypertension before or after cyclosporine. There were 56.0% children with normal renal function in steroid resistant nephrotic syndrome and 60.0% children with normal renal function in steroid toxicity NS at the end of the study over the period of 5 years (60 months).

Conclusion: Majority of the children with nephrotic syndrome treated in Hospital Universiti Sains Malaysia were steroid sensitive. Cyclosporine had been used in case of steroid resistant nephrotic syndrome and steroid toxicity nephrotic syndrome. Findings from our study found that cyclosporine is a safe drug and could be considered in the treatment of children with steroid resistant or steroid toxicity nephrotic syndrome.

CHAPTER ONE

INTRODUCTION

1 INTRODUCTION

1.1 Background of the study

Nephrotic syndrome is primarily a paediatric disorder and is 15 times more common in children compare to adult. Even though primary nephrotic syndrome is relatively rare in childhood but it causes a significant clinical burden to paediatric nephrologists. The incidence of NS is 16 cases per 100 000 child population and common in Asian children (Hudson et al., 2000). The male to female ratio is 2:1. It is usually present in preschool age (1-6 years old). Steroid sensitive nephrotic syndrome (SSNS) is the most frequent glomerular disease encountered during childhood. Steroid is still the mainstay therapy for NS. But some of the cases are resistant to steroid therapy. Even in SSNS, relapses occur up to 70% of children, with most of these patients had frequent relapses or steroid dependent (Fakhouri et al., 2003). Immunosuppressive drugs, such as cyclosporine, cyclophosphamide, chlorambucil,and levamisole have proved effective as steroid-sparing agents (Hirano et al., 2000). Renal prognosis is usually favourable in these children despite their frequent relapses. However some of these children will end-up in end stage renal failure and require renal transplant. Cyclosporine has been used in Hospital Universiti Sains Malaysia (HUSM) since 1996 but there have been no published studies on the outcomes of NS patient treated with cyclosporine in Malaysia. We need to establish our local databases and this information will be useful for our assessment and during consultation with parents. What had been published in non-local literatures may not be a real reflection for our country. This study was done to look at demographic/clinical profile of our NS children treated with cyclosporine with respect to outcome, side effect and the development of renal failure.

1.2 Nephrotic syndrome

Nephrotic syndrome results from damage to the glomeruli, the structures in the kidneys that work to filter the blood. This damage permits proteins in the blood to leak into the urine, causing proteinuria. NS is characterized by:

1. proteinuria >40mg/m^2/hour or (greater than 1g/m^2/day),

2. hypoalbuminimea (serum albumin less than 25g/l)

3. oedema.

4. hypercholesterolemia

The estimated annual incidence of NS in healthy children is 2 to 7 new cases per 100,000 children in the developed country, but it is 6 time higher in Asian country with the incidence at about 16 cases per 100 000 child population (Hudson et al., 2000). The ratio male to female is 2:1. Approximately 50% of affected children are within the range of 1 to 4 years; 75% are younger than age 10 years. NS is a recurrent disorder, so each new case likely will continue to manifest disease for some time. NS syndrome is one of the most frequent reasons for referral to a paediatric nephrologists for evaluation, although its insidious onset frequently causes delay in diagnosis (Roth et al., 2002).

The main cause of NS is primary or otherwise known as idiopathic nephrotic syndrome (INS) when the actual cause of the NS is unknown. But there is a strong evidence of immune dysregulation involving cell mediated immunity. Genetic studies also had identified several genetic mutation which lead to NS (Salomon et al., 2000). Secondary NS

is referred to genetic disorders and secondary diseases associated with drugs, infections, or neoplasia (Eddy and Symons, 2003).

The incidence of INS varies with age, race and geographical area (Srivastava et al., 1999). INS is most commonly caused by one of two diseases: minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). A third distinct type, membranous nephropathy is rare in children. Patients with INS are initially treated with corticosteroids. Majority of the NS patients responded to corticosteroid therapy. Although minimal change disease has the best response to therapy and prognosis, there is substantial clinical overlap and these conditions are thought to represent different parts of a disease spectrum rather than disorders with different pathogeneses. Experience has shown that the response to steroid therapy carries a greater prognostic weight than the histological features seen on biopsy. Therefore, two types of NS can be defined as steroid-responsive NS, in which the proteinuria rapidly resolves and steroid-resistant NS, in which steroids do not induce remission (Eddy and Symons, 2003). Several second-line drugs such as cyclosporine, cyclophosphamide and levamisole noted to be effective for complicated and steroid-unresponsive INS patients. INS is a chronic relapsing disease for most steroid-responsive patients, whereas most children with refractory FSGS ultimately develop end-stage renal disease (Eddy and Symons, 2003).

MCNS is the most common form in children. Since patients with MCNS have the highest rate of responsiveness to standard therapy and the best long-term prognosis, the separation of MCNS from others is important. More than 90% of children with minimal change disease respond to corticosteroid therapy (SSNS). 40-60% experience frequent relapses or

have steroid dependence. These children require frequent corticosteroid therapy or treatment with immunosuppressant, and are at high risk of cumulative steroid toxicity and side effects of cytotoxic therapy. Despite relapsing course, progression of MCNS to end stage renal disease is extremely rare.(Nanjundaswamy and Phadke, 2002)

Focal segmental glomerulosclerosis (FSGS) is the second most common histology subtype seen in children and appears to be increasing in frequency. Focal segmental glomerulosclerosis is defined by the histological finding of sclerosis, which affects a segment of the glomerular tuft of only some (focal) glomeruli, predominantly those in the juxtamedullary region. A renal biopsy is necessary to make the diagnosis of FSGS, because no clinical finding is specific for the underlying histology. The clinical presentation of patients with primary FSGS is proteinuria, usually severe, resulting in the nephrotic syndrome. However, FSGS can also be asymptomatic, with proteinuria detected only on routine analysis. Focal segmental glomerulosclerosis is distinguished clinically from minimal change disease by hematuria, hypertension, renal insufficiency at presentation, steroid resistance, and progressive renal insufficiency. The incidence of FSGS has been reported to be between 5% and 20% of biopsies in children presenting with INS (Matalon et al., 2000).

Membranoproliferative glomerulonephritis (MPGN) may manifest as NS, particularly in older children and adolescents. Its clinical picture is more closely associated with a nephritic picture, but sometime it may appear similar to MCNS or FSGS. Membranous glomerulonephritis (MGN) accounts for less than 1% of the cases of NS in childhood.

Congenital NS becomes a consideration when nephrosis appears during the first year of life and particularly in those instances in which the clinical syndrome starts in the first few months.

1.3 Pathophysiology

The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight respectively from approximately 6cm and 24gram in full term newborn to 12cm or more and 150gram in an adult. The kidney has an outer layer, the cortex which contain the glomeruli, proximal and distal convoluted tubule and collecting duct and an inner layer, the medulla which contain the straight portion of the tubule, the loop of Henle, the vasa recta and the terminal collecting duct. The glomeruli of the kidneys are the parts that normally filter the blood. They consist of capillaries that are fenestrated that allow fluid, salts, and other small solutes to flow through, but normally not proteins. Heavy proteinuria (albuminuria) is the hallmark and the primary abnormality in NS. The initiating event that produces proteinuria remains unknown. INS is believed to have an immune pathogenesis, and lymphocyte dysfunction has been suggested. A highly cationic plasma protein that may neutralize the anionic charge on the glomerular capillary wall has been described in nephrotic children. Investigators have noted a decrease in immune responsiveness and related this to alterations in either T-lymphocyte number and/or function. The presences of suppresser cytokines or lymphokines have been shown to have a role in the pathogenesis of the proteinuria. The rate of apoptosis in circulating T-lymphocytes also has been found to be increased, and a role for reduced antioxidant defence has been postulated. In INS, the glomerular capillary permeability to albumin is

selectively increased, and this increase in filtered load overcomes the modest ability of the tubules to reabsorb protein. At least two hypotheses are proposed to account for this increased permeability. The traditional hypothesis relates to changes in the anionic composition of the glomerular basement membrane (GBM). In the normal state, the endothelial side of the glomerular capillary is negatively charged because of the presence of a variety of polyanions along this surface. Thus, the negatively-charged protein, albumin, is less likely to be filtered.

Studies have demonstrated a decrease in the normal content of sialic acid (a polyanion) from the basement membrane and in such a state, permeability of the glomerular basement membrane would be selectively altered, increasing capillary transport of anionically charged particles such as albumin. An alternative proposal to explain the heavy proteinuria invokes a primary role for the epithelial cell podocytes. Flattening, retraction, and effacement of the podocyte foot processes are a constant feature of heavy proteinuria. It is believe that primary distortions of the slit diaphragm filaments are present and that a redistribution of nephrin from the podocyte slit pores into the cytoplasm causing massive proteinuria (Hingorani et al., 2004).

Hypoalbuminemia is the result of the increased urinary loss of protein. Other factors, however, may contribute to the hypoalbuminemia, among them decreased synthesis, increased catabolism, and increased gastrointestinal losses. The albumin synthesis rate is not decreased but the capacity to increase hepatic production appears insufficient to compensate for the large urinary losses. Oedema appears to be the natural consequence of the hypoalbuminemia. The classic explanation for oedema formation is a decrease in plasma oncotic pressure causing extravasations of plasma water into the interstitial space.

But the precise cause of the oedema and its persistence is uncertain. A complex interplay of a variety of physiologic factors (ie, decreased oncotic pressure, increased activity of aldosterone and vasopressin, diminished atrial natriuretic hormone, activities of various cytokines and physical factors within the vasa recta) probably contribute to the accumulation and maintenance of oedema.

1.4 Clinical features

The first sign in children is usually swelling of the face or periorbital oedema is a common presentation. Oedema increases gradually and become clinically detectable when fluid retention exceeds 5% of body weight. This is followed by oedema of dependent parts such as ankle; legs, scrotum and penis, or labia may also be observed. Anasarca can be the presenting symptom as well. Blood pressure is usually normal but sometimes elevated. When ascites build up rapidly, the child complain of abdominal pain and malaise. In certain instances, patients notice frothy urine, which leads to investigations that reveal evidence of NS. A hypercoagulable state leading to thrombotic complications, such as deep vein thrombosis of the calf veins or the renal vein, may be the first clue indicating NS.

1.5 Physical examination

Patients present with increasing oedema over a few days or weeks, lethargy, poor appetite, weakness, and occasional abdominal pain. Oedema is the predominant feature and initially develops around the eyes and lower extremities. With time, the oedema becomes generalized and may be associated with an increase in weight, the development of an ascites or pleural effusion, and a decline in urine output. Hematuria and hypertension are

unusual but manifest in a minority of patients. The initial episode and the subsequent relapses may follow an apparent viral upper respiratory tract infection.

1.6 Investigation

At first presentation several investigation need to be done in order to diagnose NS. These tests are listed below.

1. Full blood count
2. Renal function test
3. Serum albumin
4. Urinalysis and culture
5. Quantification for urine protein excretion (24 hour urine collection or early morning spot urine protein creatinine ratio)

If the clinical features are atypical, other investigations may include:

1. Antinuclear factor / anti ds DNA
2. Serum complements level – C3 and C4
3. ASOT (anti streptolysin O titer)
4. Other as indicated

1.7 Renal biopsy

No renal biopsy is required prior to cytotoxic therapy in children with uncomplicated SSNS (Stadermann et al., 2003). This is because about 80-85% of INS had MCNS and 93-97% of

it responds to corticosteroid therapy. The main indication for renal biopsy is SRNS. Age younger than 12 month and older than 11 years is another indication, even in patient with a typical clinical feature. Others would depend on the present of atypical features or features to suggest other renal diseases.

1.8 Management

In HUSM, the management of NS cases are according to the protocol given in national consensus standard protocol as in page 17. Children who develop NS are categorized according to their respond to corticosteroid therapy. The majority of patients go into remission and only those with steroid resistant disease or who manifest atypical clinical or laboratory features undergo a renal biopsy. Patient whom experience steroid induced remission were assumed to have MCNS and interpretation supported by recent studies in which biopsy were performed regardless of respond (Stadermann et al., 2003). HUSM is also as a regional centre for renal biopsy for east coast of Malaysia. Cases of nephrotic syndrome which required renal biopsy are referred here. Cyclosporine was commenced for selected cases, base on renal biopsy histology and other clinical presentation. Patient who has been started on cyclosporine would be on regular follow-up in HUSM with paediatric nephrologists and monitoring of side effect of the drug, remission/relapse state, cyclosporine level, urine albumin, renal function and liver function test are done according to the required protocol.

1.8.1 Corticosteroid

1.8.1.1 At Initial diagnosis

Corticosteroids is still the mainstay therapy and is effective in inducing remission of NS but the most optimal dose and duration is yet to be resolved although it has been found that longer duration results in more prolonged remission. Corticosteroids was found to be effective in inducing remission of NS from the 1940's, and has since then been used as first line therapy in the treatment of INS although no controlled trial was ever conducted about its efficacy. Controversy lies in the dosage and duration of corticosteroids used at initial diagnosis of the NS. Various regimes of corticosteroids have been used. The two regimes discussed were the modified ISKDC regime and longer initial steroid induction regime.

Modified ISKDC regime

Prednisolone dosage at:

- 60 mg/m^2/day (maximum 80 mg/day) for 4 weeks
- 40 mg/m^2/48 hours for 4 weeks only.

Long initial prednisolone regime:

Prednisolone dosage at:

- 60 mg/m^2/day (maximum 80 mg/day) for 4 weeks
- 40 mg/m^2/48 hours for 4 weeks.
- Reduced by 25% monthly over the next 4 months