LONG TERM OUTCOME OF CHILDHOOD NEPHROTIC SYNDROME

Thesis

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Introduction

Nephrotic syndrome is a primarily pediatric disorder characterized by heavy proteinuria (>40mg/m^2/hr), hypo-labuminemia (< 2.5 gm/dl), edema and hyperlipidemia **(Vogt and Avner, 2004)**.

Steroid dependent patients, frequent relapsers and steroid resistant patients are all patients with chronic form of the disease and need long term treatment with corticosteroids ***(Tune and Mendoza, 1997)***. and may need additional treatments such as cyclophosphamide, chlorambuucil, azathioprine, high dose pulse methy1 prednisolone and cyclosporine ***(Niaudet, 2004)***.

Long term outcome of steroid sensitive idiopathic nephrotic syndrome (SSNS) in children is usually considered benign with cessation of relpapses after puberty also data of follow up in adulthood are scarce ***(Röth EM et al., 2005)***.

Development of steroid dependency and or resistance represent a significant therapeutic challenge in steroid – sensitive nephrotic syndrome. Previous studies have shown conflicting results concerning the benefit of a 12week treatment with cyclophosphamide ***(CPO), (Kemper MJ et al., 2000)***.

Comparative effects of various treatment modalities remain uncertain because of the absence of head – to – head trials, but existing trial evidence is strongest for cyclophosphamide and cyclosporins ***(Hodson EM et al., 2005)***.

Aim of Study

Long term follow up of children with nephrotic syndrome to determine the long clinical outcome, complications and the long term effects of various therapeutic modalities used during the course of treatment (steroid alone ± levamisole, azathioprine, cyclo-phosphmide, cyclosporine A).

Nephrotic Syndrome

The term nephrotic syndrome describes the clinical state characterized by the presence of heavy proteinuria, hypoalbuminaemia and oedema. Although other clinicopathological findings coexist, they remain the central finding in nephrotic syndrome ***(McBryde et al., 2001)***.

Some important definitions:

Nephrotic range proteinuria is defined as proteinuria greater than 40mg/m2/h (or a protein /creatinine ratio greater than 200mg/mmol or 2.0mg/mg) ***(Clark and Barratt, 1998)***.

Remission denotes a reduction of proteinuria to less than 4 mg/m2/h or a urinary albumin dipstick of 0 or trace for 3 consecutive days ***(Clark and Barratt, 1998)***.

A relapse occurs with the recurrence of proteinuria of greater than or equal to 40 mg/m2/h or urinary albumin dipstick of 2+ greater ***(Clark and Barratt, 1998)***.

Steroid responsive patients are those patients who go into remission with steroid therapy alone ***(Clark and Barratt, 1998)***.

Steroid resistance : a failure to go into remission either (1) after 4 weeks of entral prednisone at dose of 60mg/m2/d; (2) after 4 weeks of the same dose of prednisone plus 3 intravenous doses of methylprednisone 1000 mg/1.73m^2/dose ***(Niaudet et al., 1998)***; or (3) after 4 weeks of prednisone for 4 weeks at the

same dose followed by an additional 4 weeks of alternate-day prednisone at a dose of 40 mg/m2/dose ***(ISKDC, 1981)***.

Steroid dependants: those patients who relapse while on alternative-day steroid therapy or within 28 days of stopping prednisone therapy ***(Vogt and Avner, 2008)***.

Frequent relapsers: patients who respond well to prednisone therapy but relapse $\geq$4 times in a 12 months period ***(Vogt and Avner, 2008)***.

Classification of Nephrotic Syndrome:

A) Primary idiopathic nephrotic syndrome (INS), due to renal cause; 90% of cases:

1- Minimal change nephrotic syndrome (MCNS) 80-85% of INS.

2- Focal glomerulosclerosis (FGS) 10% of INS.

3- Mesangial proliferative glomerulonephritis (MPGN) 5% of INS:

   a. With IgM deposition.

   b. With IgA-IgG deposition (Berger's disease).

4- Immune complex glomerulonephritis.

   a. Membranoproliferative.

5- Chronic glomerulonephritis.

6- Congenital nephrotic syndrome.

(Haycock, 1995)

B) N.S. Secondary to renal involvement in systemic disorders 10% of cases:

1- Henoch-Schonlein purpura.

2- Systemic lupus erythromatosus (SLE).

3- Systemic infections:

   a. Hepatitis B

b. Congenital and secondary syphilis.
c. Malaria.
d. Ventriculoatrial shunt infection.
e. Varicella.
f. Subacute bacterial endocarditis.
g. Acquired immunodeficiency syndrome (AIDs).

4- Post-infectious glomerulonephritis.

5- Cardiovascular:

a. Sickle cell anaemia
b. Massive congestive heart failure.
c. Renal vein thrombosis.

6- Diabetes mellitus

7- Drugs and toxins:

a. Gold
b. D-penicillamine.
c. Mercury.
d. Captopril
e. Heroin
f. Mercurial
g. Bismuth
h. Trimethadone

i. Propencid

j. Non steroidal anti-inflammatory drugs (NSAID).

8- Neoplasms:

a. Hodgkin's disease.

b. Leukaemia.

c. Carcinoma.

d. Multiple myeloma.

9- Chronic inflammatory disease:

a. Amyloidosis

b. Familial mediteranean fever.

10- Hereditary disorders: Alport's syndrome

11- Allergic:

a. Serum sickness.

b. Inhaled pollens.

c. Poison of bee sting.

d. Food allergy.

Quoted from ***(Cotran et al., 1994)***

Long Term Complications

Complications of nephrotic syndrome may be a direct sequence of the disease process itself or the result of treatment of the underlying process.

The most common complications of N.S. include: infections, thrombo-embolic events, malnutrition, anaemia, endocrine abnormalities, acute renal failure, hypertension and impaired growth ***(McBryde et al., 2001)***.

1- **Infections:** infection is the major complication of N.S. Children in relapse have increased susceptibility to bacterial infection because of urinary losses of immunoglobulins and properdin factor B ***(Vogt and Avner, 2008)***.

In addition patients with N.S. have decrease opsonization of bacteria as a result of decrease serum level of factor B (C3 proactivator) and D necessary for alternate complement pathway ***(Nash et al., 1992)***.

Also defective cell mediated immunity, immunosuppressive therapy, malnutrition and oedema/ ascites acting as a potential "culture media". Spontaneous bacterial peritonitis is the most frequent type of infection, although sepsis, pneumonia, cellulites, and urinary tract infection may also be seen, although streptococcus pneumoniae is the most common organism causing peritonitis, gram –ve bacteria such as Eschericia coli

may also encountered. Because fever and physical finding may be minimal in presence of corticosteroid therapy, a high index of suspicious, prompt evaluation (include culture of blood and peritoneal fluid) and early initiation of antibiotic therapy are critical, the role of prophylactic antibiotics therapy during N.S relapse is controversial all children with N.S should receive polyvalent pneumococcal vaccine (if not previously immunized). Ideally administrated when child in remission and off daily steroid therapy. Children with negative varicella titre should begin V. vaccine when in remission or on a low dose of alternate-day steroids, as live virus vaccines should not be administered until the patient is receiving <20 (mg/day) on a daily or alternate-day schedule. In those patients receiving >2mg/kg/day or (>20mg/day) on a daily or alternative day schedule, live virus vaccines should be avoided until 2 to 4 weeks after discontinuation of corticosteroids ***(American Academy of Pediatrics, 2000)***.

Non immune nephrotic children in relapse exposed to varicella should receive V.Z immunoglobulins within 72 hours of exposure. Influenza vaccine should be given on a yearly basis ***(Vogt and Avner, 2008)***.

Another opinion is that all killed vaccines are generally regarded as safe for administration when child is in remission. However, relapses are noted to cluster following meningococcal C conjugate vaccination program in the United Kingdom ***(Abeyagundwarderia et al., 2003)***.

All live vaccines should be avoided until children are off steroids for at least 6 weeks. Additionally they should be avoided when cyclophosphamide or CSA therapy have been initiated ***(Royal College of Physicians, 1994)***.

2) Thromboembolic events:

Children with N.S are at increase risk of thromboembolic events ***(Vogt and Avner, 2008)***. Although thromboembolic complications occur less commonly in pediatrics than in adult patients with N.S, they still constitute a severe and potentially life threatening complication ***(McBryde et al., 2001)***.

The incidence of thromboembolic complications in N.S have been reported to be approximately 3% but with pulmonary embolism reported to be as high as 28% in patient with steroid dependant subtype ***(Sumboonnanonda et al., 2005)***. Autopsy analysis has shown that 38% of children with renal vein thrombosis were represented with N.S. subclinical pulmonary embolism was found in 28% of children with N.S by scintigraphic pulmonary ventilation and perfusion study.

In children with N.S, nearly 20% of thromboembolic events are arterial in nature, and the risk of thromboembolic events in patient with SRNS is twice that of patient with steroid responsive N.S. The most commonly involved vessels are the deep veins of the legs, followed by the inferior vena cava, with other reported episodes of vascular thrombosis occurring in the

renal veins, superior vena cava, the mesenteric a, hepatic veins and middle cerebral arteries ***(Lilova et al., 2000)***.

Multiple abnormalities in the coagulation pathway are observed in N.S. The hypercoagulable states and the TEC in N.S. are attributed to a loss of intermediate size antithrombine protein (AT III) in the urine as a direct result of heavy proteinuria. However, there is increase in the pro-coagulation serum proteins (factor I, II, V, VII, VIII, X, and XIII) due to their increased hepatic synthesis. A significant increase in protein C activation in NS patient represents a protective mechanism against thrombosis. The firinolytic system also plays an important role in preventing thrombosis in these patients. In addition congenital abnormalities of coagulation factors and N.S. may simultaneously be associated with hypercoagulable status can be classified as acquired, for example, if they arise as a consequence of the heavy proteinuria; or inherited, if only causally associated to N.S. Therefore, TEC could be due to combined low plasma ATIII, protein S and protein C deficiency, albumin, high fibrin and cholesterol levels, the levels of protein S, protein C and AT III are frequently decreased in N.S because of their loss in urine. Furthermore, anticoagulant protein S and protein C in the serum may also remain functionally inactive because of an increase in the hepatic synthesis of binding proteins for protein S and protein C. TEC may result from an increase in both the plasma fibrinogen levels and platelet count. However, platelets are

dysfunctional and often increase in number in N.S increase platelet hyperaggregability may be due to increase platelet synthesis of thromboxane in response to the hypoalbuminemia. An important cause of thrombosis in N.S. that should be always in mind, is volume depletion, especially iatrogenic through over vigorous diuresis. The risk of TEC in N.S is increase by hyperviscosity of the blood caused by hyperfibrinogenaemia, intravascular volume depletion resulting from inappropriate use of diuretics ***(Zaffanello and Franchiri, 2007)***.

Prophylactic anticoagulation is not recommended in children unless they have had previous thromboembolic events. Over aggressive diuretics should be avoided and use of indwelling catheters limited because these may increase the likelihood of clotting complication ***(Vogt and Avner, 2008)***.

Also, predisposing factors, personal and family history of TEC, thrombosis location and evolution should be always investigated in children with N.S. adequate therapy with anticoagulant and fibrinolytic drugs should be recommended in children with acute symptoms, in as much as prophylaxis is necessary in relapsing patients.

3) Malnutrition:

Because of proteinuria and increased protein catabolism, children with the nephrotic syndrome are in a state of negative nitrogen balance when they relapse. Although increasing dietary protein transientry increases the serum total proteins, it