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Continuous Medical Education

Idiopathic nephrotic syndrome and the immune system

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Childhood nephrotic syndromes are most commonly caused by one of two idiopathic diseases: minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). The cause of idiopathic nephrotic syndrome (INS) remains unknown, but evidence suggests that it may be a primary T-cell disorder that leads to glomerular podocyte dysfunction[1].

In 1974, Shalhoub postulated that INS might be secondary to a disorder of T-lymphocyte function[2]. He hypothesized that clonal expansion of a T-lymphocyte subpopulation might result in the production of lymphokines, which increase the permeability of the glomerular filtration barrier to proteins. Data supporting this hypothesis were the response of the disease to corticosteroids and alkylating agents; the remission occurring in association with measles, which depresses cell-mediated immunity; the susceptibility of patients to pneumococcal infections; and the occurrence of MCNS in patients with Hodgkin's disease[3].

A 3-4-fold increased incidence of HLA-DR7 in children with INS has been reported[4,5]. An association with HLA-B8 was reported in Europe. Children with atopy and HLA-B12 have a 13-fold increased risk of developing INS[3].

Two observations provide important clues to the primary pathophysiology of INS. A plasma factor may alter glomerular permeability, especially among patients with steroid-resistant nephrotic syndrome (SRNS). Altered T-lymphocyte responses seem to be important; a primary T-cell event could result in the production of a permeability factor that interferes with the expression and/or function of key podocyte proteins to cause proteinuria[1].

A soluble factor produced in nephrotic syndrome has long been proposed to mediate changes in the capillary wall and lead to albuminuria[6,7]. The most compelling evidence comes from experience with renal allografts. Nephrotic syndrome disappears when an MCNS kidney is transplanted into a patient without nephrotic syndrome; FSGS may recur (frequently within hours) when a normal kidney is transplanted into a patient who has end-stage renal disease due to FSGS[8].

Possible immunological basis for nephrotic syndromes

The putative permeability factor seems to be derived from lymphoid cells. The association of nephrotic syndrome with primary immunological disorders such as lymphoma, leukemia, thymoma, Kimura's disease, and Castleman's disease, and therapeutic agents such as interferon support this hypothesis. Cultured T cells isolated from nephrotic patients have been reported to synthesize a factor or factors that produce transient proteinuria when injected into rats[9] or impair glomerular podocyte synthesis of glycosaminoglycans[10]. Still unclear is whether MCNS can occur as a manifestation of a primary allergic disorder. Although several anecdotal case reports have been published and serum IgE concentrations are frequently increased in nephrotic syndrome, therapeutic approaches based on the identification and elimination of the triggering allergen are rarely effective[11, 12].

In response to an apparent rising incidence of FSGS, investigators have used modern molecular diagnostic tools to identify a possible infectious cause for FSGS. Such studies have provided insights into HIV nephropathy, which shows the presence of HIV genome in renal tubular cells and podocytes[13]. Other viral genomes have been identified in patients who have apparent idiopathic FSGS, including parvovirus (erythrovirus) 19[14], Simian virus 40 (SV40)[15], and hepatitis C[16].

EFFECTS OF NEPHROTIC SYNDROME ON THE IMMUNE SYSTEM

Serious infection, especially cellulitis and spontaneous bacterial peritonitis, can complicate nephrotic syndrome. The rate of peritonitis is 2-6%[17], and overwhelming infection carries a mortality rate of 1.5%[18]. Susceptibility to bacterial infection is related to multiple predisposing factors. Impaired complement-dependent opsonisation delays clearance of encapsulated micro-organisms, especially *Streptococcus pneumoniae*[19]. Patients are also predisposed to gram-negative bacterial infections[20]. Other factors include altered T-cell function, altered IgG concentrations (total and subclass changes), immunosuppressive therapy, and mechanical factors (edema, ascites) [3].

Since many children with idiopathic nephrotic syndrome are varicella non-immune, varicella exposure and infection require special consideration[21]. Prophylactic treatment with varicella zoster immune globulin is recommended for non-immune patients taking immuno-suppressive treatments[22]. Concomitant use of oral acyclovir may also prevent serious varicella infection in patients receiving corticosteroids[23].

Cellular immunity

Cell-mediated immunity is depressed in patients with INS and returns to normal with remission[24]. Peripheral blood T-lymphocyte subpopulations have been shown to be altered in children during replapse[25]. Increased expression of the interleukin (IL)-2 receptor on the T-lymphocyte surface is found in patients with MCNS during relapse but not during remission[26].

Humoral immunity

Patients with MCNS have depressed serum IgG levels. This is more pronounced during relapses but persists during remission[27]. Conversely serum IgM is elevated. Altered serum levels of IgG and IgM maybe secondary to abnormal T-cell regulation of Ig synthesis[28]. Factors B and D (cofactors of the alternative pathway of the complement) are decreased during relapses due to urinary loss but return to normal during remission[3].

IMMUNIZATIONS IN NEPHROTIC SYNDROME

Prophylaxis of *S. pneumoniae* with oral penicillin is often prescribed to children during initial corticosteroid treatment[3], but few data support this practice[29]. Although antibody response to pneumococcal vaccine is blunted in children with steroid responsive nephrotic syndrome, vaccination with the conjugated pneumococcal vaccine is recommended[30].

Once remission is achieved, immunization with varicella vaccine seems safe and effective, although additional doses may be required to achieve full immunity[31, 32].

It is well known that both active immunization and infectious diseases may induce the nephrotic syndrome. Despite this, vaccination against viral hepatitis type B in nephrotic children is highly recommended, since it influences favorably the further clinical course of the syndrome by protection from the disease[33].

It was demonstrated that pediatric patients with NS have an adequate antibody response to influenza A vaccine[34]. An important observation was reported by Abeyagunawardena et al. [35] when in November, 1999, all children under age 18 years in the UK were offered immunization with the newly introduced meningococcal C conjugate vaccine (MCCV). In a cohort of 106 patients with nephrotic syndrome, there were 63 relapses during the 12 months before vaccination, and 96 during the equivalent period postvaccination. The relapse rate of nephrotic syndrome increased significantly after administration of MCCV. They concluded that vaccination of such children needs to be carefully considered.

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