Management of the Nephrotic Syndrome

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The nephrotic syndrome represents one of the major clinical problems in nephrology. It is usually defined as the constellation of clinical findings which includes edema, massive proteinuria, low serum albumin, high serum cholesterol, and the presence of oval fat bodies in the urine.[1] However, if we focus on the primary disturbance in the patient, that is, massive proteinuria, the nephrotic syndrome may be defined more simply as the clinical and metabolic consequences of persistent and massive proteinuria. The other manifestations listed in the classic definition are all inconstant and secondary to this loss of protein and may be found in other clinical disorders. Proteinuria is considered massive when it is greater than 3.5 mg/kg body weight per day, and persistent when present for many weeks or months. For diagnosis of the nephrotic syndrome, 24-hour urine protein excretion must be measured; a spot measurement is inadequate because some patients with massive proteinuria produce occasional specimens with little or no protein.

In understanding potential causes of the nephrotic syndrome, it is useful to recognize two general categories of disease.[2,3] One is the nephrotic syndrome associated with systemic illnesses. The other is not associated with a recognizable systemic process, and thus reflects only intrinsic renal disease. The most common systemic diseases associated with the nephrotic syndrome are diabetes mellitus, systemic lupus erythematosus, malignancy and amyloidosis. Additionally, there is a large variety of other diseases less commonly associated with the nephrotic syndrome. Many of these involve immune and toxic reactions related to drugs, as well as infectious and environmental agents. Although these entities are uncommon, it is important to recognize them, as removal of the drug or toxin, or definitive treatment of the infection, is a fundamental part of the management of these patients. Drugs shown to be associated with the nephrotic syndrome include the antiepileptic drugs paradione and tridione, anticoagulant agents, and penicillin. Forms of allergic reactions associated with the nephrotic syndrome include those following bee sting or exposure to poison oak or poison ivy. Chronic infections which are known to be complicated by the nephrotic syndrome include syphilis, malaria, hepatitis and toxoplasmosis.

There are several intrinsic renal diseases which cause the nephrotic syndrome. Recognition of these depends on characteristic morphologic findings in the renal biopsy specimen. The first is the clinicopathologic entity referred to as nil disease or lipoid nephrosis.[2] As implied in the term nil disease, there is little, if any, change in the normal architecture of the kidney when examined by light microscopy; however, electron microscopy does disclose changes of epithelial foot process fusion. Nil disease is the predominant cause of the nephrotic syndrome in children, particularly between ages 2 and 5 years; it is a less common cause in adults, accounting for approximately 15% of adult cases of primary nephrotic syndrome.

The second intrinsic renal disease which causes the nephrotic syndrome is a condition termed idiopathic membranous glomerulopathy[2] and it is found most frequently in adults. This term refers to the morphological changes of diffuse thickening of the basement membrane of all glomeruli. Within and to

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the outside of the basement membrane are found desposits which have been shown to contain immunoglobulins and serum complement components. They are thought to result from the deposition of circulating complexes of antigen and antibody, and are responsible for injury to the glomerulus which results in heavy proteinuria. Membranous glomerulopathy accounts for approximately 40% of the primary nephrotic syndrome in adults. It is relatively uncommon in children in the United States.

A third intrinsic renal disease which causes nephrotic syndrome is termed membranoproliferative glomerulonephritis.[3] In this disease the mesangial or supporting cell of the glomerulus is affected. Although the cause of this disease is not understood, immune deposits may be found in the mesangial area. This is an uncommon cause of nephrotic syndrome in adults but is perhaps the most common cause in patients aged 10 to 20 years. Prognosis for this disease is not good as its course commonly leads to renal failure.

The fourth intrinsic disease recognized as causing the nephrotic syndrome is termed focal sclerosing glomerulonephritis.[2,3] As this pathologic term indicates, the lesion involves a process which at first is confined only to parts of individual glomeruli. Again, the cause is unknown, although immune deposits are found in the areas of scarring. Like membranoproliferative glomerulonephritis, this disease also frequently results in renal failure.

In managing patients with the nephrotic syndrome, it is useful to bear in mind the pathophysiology of the syndrome. Although the most frequent concern is with the development of massive edema, it should be remembered that such edema is a consequence of massive loss of protein into the urine. This in turn leads to depletion of intravascular albumin and reduction of plasma oncotic pressure. In turn, fluid escapes from the vascular compartment into the interstitial tissue. As a compensatory response to the fall in plasma volume, there is decreased salt and water excretion by the kidney which may further increase the accumulation of edema. If intravascular albumin depletion can be prevented or reversed, significant problems with edema and fluid retention will not develop. As albumin depletion is caused primarily by loss through a leaky glomerulus, the first approach, if possible, should be to reverse the albumin leak. As we shall see later, this is regularly accomplished only in nil disease in which the leak is predictably corrected by steroids. In other conditions in which the albumin leak is not remedial, metabolic considerations should be first and foremost in management. A high-protein and high-caloric diet can result in significant repletion of intravascular albumin.[5] To the extent that albumin loss can not be matched by increased dietary protein, then salt restriction and diuretics may be necessary to prevent undue accumulation of edema. From a practical standpoint, the diet of the nonazotemic patient should contain a minimum of 100 gm of high-quality protein and approximately 3,500 calories for the average nephrotic adult. At times, protein intake of 2-3 gm/kg of body weight will be required. Since many of these patients are anorectic and have been grossly malnourished for some time, the diet may have to be increased gradually until these goals are accomplished. This will require persistent and close cooperation between the patient, the physician, and the dietitian.

If serum albumin remains severely depressed despite optimal intake of protein, it is probable that salt and water restriction, as well as diuretics, may be necessary for control of severe edema. One must remember that, although there may be massive accumulation of edema, there is at the same time potential for significant intravascular volume depletion. Therapy designed to reduce edema accumulation may further reduce intravascular volume, and potentially result in shock. Judicious use of salt restriction and diuretics is necessary in order to achieve the appropriate balance in which severe accumulation of edema is prevented without unduly jeopardizing intravascular volume. In general, this involves sodium restriction of approximately 40-60 mEq/p day. Diuretics should be adjusted so that edema is not reduced to the point where postural changes in blood pressure and pulse occur. Although this may involve some trial and error, one can usually arrive at a body weight in which massive edema is prevented but not at the expense of severe volume depletion.

The nephrotic syndrome may also be complicated by increased susceptibility to infection. Prior to the introduction of steroid and antibiotic therapy, pneumococcal pneumonia and/or peritonitis was a major cause of death in nephrotic children. This is at least in part because of loss of immunoglobulins in the urine. In addition, protein malnutrition and edematous tissue may contribute to reduced host defenses. It is not always possible to prevent the loss of immunoglobulins in the urine of patients with persistent, heavy proteinuria, but massive edema and malnutri-

tion are potentially correctable. It is most important that the physician be alert to early signs of infection in these patients so that they are treated definitively and aggressively.

An increased thromboembolic tendency is an additional potential complication of the nephrotic syndrome. Although the mechanism is not clearly understood, there are data to suggest that a hypercoagulable state may exist in association with the nephrotic syndrome. Care should be taken that other factors, such as venous stasis, which predispose to thromboembolism, be avoided in order to minimize this risk. It is also important that those providing medical care for these patients be especially attuned to this problem, so that definitive diagnosis and treatment may be accomplished at the earliest possible time. There appears to be no basis for use of anticoagulant agents except in documented episodes of pulmonary embolus. For unclear reasons, there seems to be a predilection for the formation of clots within the venous system of the nephrotic kidney. Again, it appears that anticoagulants are not indicated except in the occurrence of a pulmonary embolus.

It has been conclusively demonstrated that patients with long-standing nephrotic syndrome may develop accelerated atherosclerotic disease, leading to an increased risk of coronary artery disease and acute myocardial infarction; this appears to be related to prolonged hyperlipidemia. There is an inverse relationship between serum albumin and serum lipid levels. Any maneuver which improves the serum albumin level, such as correction of protein malnutrition, can be expected also to lower serum lipid levels. Treatment with clofibrate does not appear to be highly effective in treating hyperlipidemia associated with the nephrotic syndrome and may be associated with severe side effects if the dosage is not reduced to correspond to the reduced serum albumin levels.

The most fundamental concern in management of the nephrotic syndrome should be the correction of increased glomerular protein leakage. If protein loss can be reversed, all secondary problems will resolve. Two general considerations relate to abnormal protein leakage. First, the physician should be aware that the nephrotic syndrome could be a manifestation of some reversible systemic process. Any drug, toxin, or allergen which could potentially cause the nephrotic syndrome should be removed, if possible. Systemic diseases associated with the nephrotic syndrome, such as malignancy and chronic infections, should be identified and treated definitively. Even when malignancy is not curable, reduction in tumor mass may lead to resolution of the nephrotic syndrome.

The second approach to treatment of glomerular protein leakage involves the use of steroids and immunosuppressant agents. It has been shown conclusively in only one disease, nil disease, that these agents can predictably reverse glomerular leakage of protein; for the rest there is little evidence of efficacy of such agents. In nil disease, treatment with prednisone, in doses of 40-60 mg/day/m^2 body surface area in children and 1 mg/day/kg body weight in adults, will result in a significant reduction in the level of proteinuria within 7 to 28 days. In general, children will respond quickly, and their proteinuria will fall off rapidly to undetectable levels. Adults tend to respond more slowly and less completely but will usually have less than 1 gm of protein excretion per day within the first 28 days of treatment. After clearing or significant reduction in the level of proteinuria, treatment is usually switched to an alternate-day regimen and the steroids reduced and subsequently discontinued over the next two to three months. Immunosuppressant agents, such as cyclophosphamide, may be useful in some patients with nil disease who have frequent relapses upon cessation of steroid therapy. Recent evidence suggests that these agents may prevent or reduce the frequency of such relapses.

In addition to the beneficial effect of steroids and immunosuppressant agents on the proteinuria of nil disease, there is also a recent and ongoing interest as to whether these agents may prevent or slow the rate of progression of renal failure in glomerulonephritis associated with the nephrotic syndrome. The severe glomerulonephritis of systemic lupus erythematosus, as well as idiopathic membranous and membranoproliferative glomerulonephritis, are diseases whose prognosis may be improved by these agents; however, studies supporting such conclusions have not been adequately controlled and remain controversial.

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