Long-Term Outcome of Children with Steroid-Sensitive Idiopathic Nephrotic Syndrome

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In children, the most frequent glomerular disease is idiopathic nephrotic syndrome, which is defined by the combination of a nephrotic syndrome and nonspecific histologic abnormalities of the kidney including minimal changes, FSGS, and diffuse mesangial proliferation. The term minimal-change disease has become synonymous with steroid-sensitive idiopathic nephrotic syndrome, although renal biopsy is usually not performed for patients who respond to steroid therapy. Indeed, the response to steroid therapy carries a greater prognostic weight than the histologic features seen on initial renal biopsy.

Up to 80% of children with idiopathic nephrotic syndrome respond to corticosteroids, with a complete remission occurring within 30 d. Approximately one third of these patients have only one attack and are definitively cured after the course of corticosteroids. Ten to 20% of patients experience relapses several months after stopping the treatment and a cure takes place after three or four episodes, which respond to a standard course of corticosteroids. The remaining 40 to 50% of patients experience frequent relapses either as soon as steroid therapy is stopped (frequent relapsers) or when the dosage of steroids is decreased (steroid dependent). These steroid-dependent patients may have a prolonged course. In the long term, the risk for relapse and the adverse effects of the treatments remain the main concerns.

There are few studies regarding the long-term outcome in adult patients with steroid-dependent nephrotic syndrome that started during childhood. Studies from the 1980s reported that no more than 10% of children had additional relapses in adulthood (1,2). More recent surveys indicated a relapse rate after 18 yr of age between 27 and 42% (3–5). Among the risk factors of relapses during adulthood are a young age at onset, a high number of relapses during childhood, and the use of alkylating agents and cyclosporine.

Whereas corticosteroids and alkylating agents were the only drugs available for the treatment of idiopathic nephrotic syndrome 30 yr ago, there have been major changes in the therapeutic approach to steroid-dependent nephrotic syndrome during the past 20 yr with the introduction of cyclosporine, levamisole, mycophenolate mofetil, and, more recently, rituximab. Therefore, the adverse effects of treatments that are given to children have changed over the years.

The study by Kyrieleis et al. (6) concerns the adverse effects of immunosuppressive treatments in 15 patients who had childhood-onset idiopathic nephrotic syndrome and still had active disease after the age of 16 yr. The two major limitations of the study are the small number of patients and their age range, with five patients aged ≤20 yr. Indeed, one may anticipate that the long-term complications are different in patients who are older than 30 yr and have still active disease.

Long-term steroid therapy that is started in childhood is associated with a number of significant adverse effects, mainly short stature, excess weight, osteoporosis, and cardiovascular events. The occurrence of growth retardation or excess weight, despite the administration of corticosteroids on an alternate-day basis, are indications for the use of steroid-sparing agents. This may explain why nowadays such complications are fairly rare, as noted by Kyrieleis et al. (6). Osteoporosis was observed in four of 11 evaluated patients. A high incidence of osteoporosis was also reported by Fakhouri et al. (3), and these findings indicate the need for further studies regarding the prevention of steroid-induced osteoporosis in children. A comparative study of 195 control subjects and 60 children and adolescents who had idiopathic nephrotic syndrome and were treated with alternate-day steroid therapy for an average of 53 mo at a mean cumulative dosage of 23,000 mg found no difference in bone mineral content as evaluated by dual-energy x-ray absorptiometry (7). Longer durations of steroid therapy in patients who relapse in adulthood may increase the risk for osteoporosis.

The high incidence of hypertension found in the series of Kyrieleis et al. (6) may be explained by the fact that most of them were still receiving steroid therapy and/or calcineurin inhibitors. Knowing the long-term effects of corticosteroids on the cardiovascular system, it will be important to know whether these patients’ hypertension remains after stopping the treatments for the nephrotic syndrome.

Long-term toxicity of alkylating agents includes gonadal toxicity. The risk for sterility is greater in boys than in girls. The cumulative threshold dosage above which oligo/azoospermia may be feared is between 150 and 250 mg/kg (8–10). Azoospermia is reversible in some patients (11), and there is no definite sperm count that can discern fertile and infertile males (12). In the study by Kyrieleis et al. (6), sperm analysis was available for
only eight patients. The authors did not find a correlation between the cumulative dosage of cyclophosphamide and the risk for sperm abnormalities; however, among the four patients who received a cumulative dosage of cyclophosphamide >330 mg/kg, the proportion of abnormal forms was increased in one patient and sperm analysis was not performed for two other patients.

Overall, the renal outcome of children with steroid-dependent nephrotic syndrome is excellent as long as patients remain steroid responsive; however, many of them receive cyclosporine, which may be detrimental to renal function in adult patients who experience relapse. The patients described by Kyrieleis et al. (6) received cyclosporine during 7 to 174 mo. The authors found that all patients had normal creatinine clearance as measured by the Cockcroft-Gault formula. These findings do not exclude that the patients developed lesions of chronic nephrotoxicity. Indeed, such lesions may develop without any appreciable decline of the GFR (13,14). For this reason, we recommend sequential renal biopsies for patients who receive cyclosporine for periods of >18 to 24 mo.

Although the long-term outcome of the disease is favorable, this chronic disease and the adverse effects of the treatments often have detrimental effects on the quality of life of children and their families. Noncompliance is probably frequent, particularly during adolescence, and contributes to relapses.

Disclosures

None.

References
