CHILDREN WITH STEROID-SENSITIVE NEPHROTIC SYNDROME COME OF AGE: LONG-TERM OUTCOME

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Objective **Long-term outcome of steroid-sensitive idiopathic nephrotic syndrome (SSNS) in children is usually considered benign, although data on follow-up into adulthood are scarce. The aim of this study was to investigate adults who had childhood SSNS regarding their relapse rate, growth, and renal and extrarenal morbidity.**

Study design **Adult patients (n = 42, 26 males) were evaluated at a median age of 28.0 (18.1 to 46.9) years and a median follow-up of 22.0 (2.9 to 39.0) years since diagnosis.**

Results **Fourteen of 42 (33%) patients relapsed in adulthood. The number of relapses during childhood and adolescence and a complicated course—administration of steroid-sparing medication such as cyclophosphamide, chlorambucil, and cyclosporin A—were identified as risk factors. Final adult height (median SD score −0.4, range −3.3 to +1.3) and body mass index (BMI) were normal. Renal function was normal in all patients, and overall morbidity was low. Only eight patients (three males) had children. Cytotoxic therapy was identified as a major factor contributing to childlessness.**

Conclusion **Relapses in adulthood were common in pediatric patients with SSNS. Growth and renal function were normal, and overall morbidity was low. Yet, transition to an adult nephrologist is recommended for all children with relapsing SSNS.** ***(J Pediatr 2005;147:202-7)***

The idiopathic nephrotic syndrome of childhood is characterized by steroid responsiveness in ≥90% of cases.[1] Despite response to corticosteroids, up to 60% of patients with steroid-sensitive nephrotic syndrome (SSNS) develop a frequently relapsing or steroid-dependent course with significant impact not only on the patient's health but also on quality-of-life and psychosocial adaptation.[1-4] Previous data suggested that long-term prognosis of SSNS is excellent as renal function remained normal and by the end of puberty >90% of patients entered long-term remission with no further relapses.[5,6] This has recently been challenged by surveys indicating a higher relapse rate in adulthood between 27% and 42% despite an array of potent immunosuppressive drugs.[7,8] For appropriate counseling of pediatric SSNS patients and their parents, accurate data on relapse rate of SSNS in adulthood are needed with special attention to potential risk factors.

Children with SSNS undergoing long-term and repeated treatment with glucocorticoids are at risk of adverse drug effects, in particular growth retardation and obesity.[9,10] Furthermore, there are concerns that cytotoxic treatment with cyclophosphamide (CPO) or chlorambucil (CLA) may result in infertility and neoplasia.[11] However, no clinical data on final height, overall morbidity, and fertility are available.[12]

The aim of our study was to obtain detailed data on long-term prognosis in SSNS. This included a detailed analysis of: (1) relapse rate into adulthood, risk factors for relapses in adulthood, and renal function; (2) long-term extrarenal morbidity; and (3) adverse drug effects, especially steroid toxicity (growth retardation and obesity) and infertility and malignancies.

APN	Arbeitsgemeinschaft für Paediatrische Nephrologie	ISKDC	International Study of Kidney Disease in Children
BMI	Body mass index		
CLO	Chlorambucil	SSNS	Steroid-sensitive idiopathic nephrotic syndrome
CPO	Cyclophosphamide		

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METHODS

Patients

Between 1970 and 2003, 138 children (93 males) with SSNS presented at the University Children's Hospital Zurich, a primary and tertiary care center for renal diseases. Using the clinic's data file system, 61 patients >18.0 years of age were identified. Two of 138 patients had died, one as a result of sepsis during a relapse at 7 years of age, the other in an traffic accident. Of these 61 adult patients, outcome data on 42 (69%) were available for evaluation. These 61 patients were followed at our institution to 20 years of age. Medical records were reviewed to collect relevant data on the course of disease, ie, number of relapses, medications, and doses. In addition, the log books, kept by all patients and providing continuous and detailed information on both daily urine dipstick testing and exact account of doses and duration of medication prescribed, were thoroughly checked.

Information regarding the outcome of patients in adulthood (≥18 years of age) was acquired by a detailed questionnaire, filled in either during a separate visit in our outpatient clinic or during a structured interview phone call to the patients and/or their adult physicians. The questionnaire consisted of detailed issues regarding: (1) health (number of relapses and medication since the last outpatient clinic visit, adverse effects of medication, occurrence of malignancy or symptomatic cardiovascular disease) and (2) family status (marriage, partnership, number of children, age at birth of the first child). All patients had regular visits at an ophthalmologist, and the results were based on the most recent report.

The information was validated using data of the personal log book and the medical records to minimize potential bias. The study was approved by the local ethical committee, and written informed consent was obtained from all patients.

To avoid selection bias we analyzed the 19 patients in whom follow-up into adulthood was not possible: Nine had moved and could not be contacted, one had died in a traffic accident, and nine patients did not consent to participate. These 19 patients did not significantly differ from the 42 evaluated patients regarding demographic data, steroid dependency, and cytotoxic therapy.

Definitions

Nephrotic syndrome was defined by urinary protein excretion of ≥40 mg/m^2/hour and hypoalbuminemia of <25g/L, according to the criteria of the International Study of Kidney Disease in Children (ISKDC).[1] Remission of nephrotic syndrome was characterized by disappearance of albuminuria (dipstick testing 0 to trace), whereas relapse was defined as reappearance of proteinuria (dipstick testing ≥2+ for at least 3 consecutive days). Frequent relapses were defined according to the ISKDC criteria (more than two relapses in the initial 6 months after presentation or more than four per year during follow-up).[13] Steroid dependency was defined according to the guidelines of the Arbeitsgemeinschaft für Paediatrische Nephrologie (APN) (at least two relapses during alternate day treatment with prednisone or within 2 weeks of cessation).[14]

Overweight was characterized by a body mass index (BMI) >25 in both men and women; a BMI >30 was defined as obesity. Height was measured using a Holtain Stadiometer (Holtain Ltd., Crymech, Dyfed, UK) with an accuracy of 0.1 cm. Short stature was defined as height less than −2 SD compared with normal stature for age and sex of Swiss children.[15] Target height was determined as following: Target height (cm) = mean parental height (cm) ± 6.5 cm for boys and girls, respectively, with a 95% CI of ± 8.5 cm.[16] Pubertal development was not recorded in all patients.

Treatment Protocols

The initial episode was treated with different regimes of steroids, depending on the date of the first manifestation, ie, patients with onset between 1970 and 1980 (n = 16) were treated with the standard initial therapy of the ISKDC,[1] consisting of daily prednisone 60 mg/m^2 body surface area for 4 weeks, followed by 4 weeks of 40 mg/m^2 on 3 days per week (intermittent regime). Between 1980 and 1990, 20 patients were treated with the standard initial therapy of the APN, where 4 weeks of prednisone 40 mg/m^2 per day were followed by 40 mg/m^2 given on alternate days.[17] Two further patients had the more recent standard therapy of the APN, consisting of 60 mg/m^2 prednisone for 6 weeks, followed by another 6 weeks of 40 mg/m^2 on alternate days. Four patients—primarily treated by local pediatricians—were given 4 weeks of high-dose prednisone, followed by various tapering on alternate days.

Relapses were treated with daily prednisone of 60 mg/m^2 until remission (0 or trace dipstick testing on 3 consecutive days) was achieved, followed by 4 weeks of 40 mg/m^2 on alternate days. In steroid-dependent patients, maintenance alternate day prednisone was instituted, and the alternate dose was gradually tapered to determine each patient's individual threshold at which relapse occurred.

Indications for alternative treatment, ie, CPO, cyclosporin A (CsA), or CLA were as follows[18]: (1) frequent relapses or mild steroid dependency (ie, <1 mg/kg per 48 hours) *and* significant psychological, behavioral, or somatic side effects, and (2) severe steroid dependency (≥1 mg/kg per 48 hours). CPO, introduced in 1967 and always the first cytotoxic course, was administered in an 8-week course, and from 1988 on in a 12-week course, according to the criteria of the APN.[14] CsA has been used since 1987 at a dose of 5 mg/kg, aiming at whole blood trough levels of 100 to 150 μg/L. CsA was restricted to patients who developed recurrent steroid dependency after a course of cytotoxic treatment. Before the introduction of CsA, CLA was restricted to a small number of patients undergoing a second cytotoxic course (daily dose 0.2 mg/kg for 8 weeks). Recently, CLA has been used as a last resort in patients with CsA failure in a daily dose of 0.15 mg/kg for 12 weeks.[19]

No patient was given human growth hormone. One male with delayed puberty was administered testosterone for