Long-Term Outcome of Biopsy-Proven, Frequently Relapsing Minimal-Change Nephrotic Syndrome in Children


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Background and objectives: Frequently relapsing and steroid-dependent minimal-change nephrotic syndrome (MCNS) that originates in childhood can persist after puberty in >20% of patients. These patients require immunosuppressive treatment during several decades of their life. We examined long-term adverse effects of persistent nephrotic syndrome and immunosuppressive medications, focusing on renal function, growth, obesity, osteoporosis, hypertension, ocular complications, and fertility in adult patients with biopsy-proven childhood-onset MCNS. Molecular analysis was performed to evaluate a possible association of a complicated course of MCNS with podocyte gene mutations.

Design, setting, participants, & measurements: We performed a prospective clinical examination of 15 adult patients that included serum and urine analysis; dual-energy x-ray absorptiometry; ophthalmologic examination; semen examination; and molecular analysis of \( NPHS1, NPHS2, CD2AP, \) and \( ACTN4 \) genes.

Results: All patients had normal GFR. Most frequent long-term complications were hypertension (in seven of 15 patients) and osteoporosis in one third of patients. Oligozoospermia was found in one patient, reduced sperm motility in four of eight patients, and teratozoospermia in six of eight patients. Ophthalmologic examination revealed myopia in 10 of 15 patients and cataract in three of 15 patients.

Conclusions: Children with MCNS that persists after puberty are at risk for complications such as osteoporosis, hypertension, cataract, and sperm abnormalities. Our study underscores a need for more effective and less toxic therapies for relapsing MCNS.


M

inimal-change nephrotic syndrome (MCNS) accounted for 77% of all cases of childhood nephrotic syndrome in a series of the International Study of Kidney Diseases in children (1). In general, long-term outcome of this disease is favorable, and treatment with prednisone leads to complete remission in one third of patients (1,2); however, 30% of these children develop a frequently relapsing course (FRNS) (1). In this case, patients are treated with cyclophosphamide (CP). If relapses persist afterward, then treatment with cyclosporin A (CsA) is given, which allows tapering of the steroid dosage but frequently leads to CsA dependence, necessitating long-term immunosuppressive treatment. The percentage of childhood MCNS that relapses in adulthood varied from 10 to 40% in the recent studies (2–4). There are few data about the long-term prognosis in this group of patients, especially concerning possible adverse effects of the immunosuppressive medication.

Although mutations in proteins expressed by glomerular podocytes were demonstrated in up to 30% of children with steroid-resistant FSGS (5,6), it remains undetermined whether underlying genetic alterations determine the susceptibility for MCNS or predispose for a more severe course of the disease. The aim of this study was to evaluate the long-term outcome of children with biopsy-proven MCNS that persisted after puberty.

Materials and Methods

Of 103 patients who had biopsy-proven MCNS and were referred to our tertiary care center because of FRNS from 1971 until 2005, we identified 78 patients who were aged ≥16 yr. Thirteen patients were lost to follow-up. Of 65 patients 19 (29%) had at least one relapse of NS after puberty. Of the latter group, 15 patients with still relapsing MCNS agreed to participate in our study. Our institutional ethical board approved the study. The clinical records of the patients were reviewed. Complete remission of NS was defined as a reduction in urinary protein excretion rate to <4 mg/m² per h or proteinuria <0.2 g/10 mmol creatinine or by 0 to trace albuminuria on dipstick during 3 consecutive days. Partial remission was defined as protein excretion...
between 0.2 and 2 g/10 mmol creatinine without hypoalbuminemia. A relapse-free period of a minimum of 2 yr without immunosuppressive medication was defined as a permanent remission. Patients were classified as frequent relapers when they experienced four or more relapses in a 12-mo period.

Baseline Clinical and Laboratory Characteristics of the Patients

Baseline clinical data, serum examination (urea, creatinine, glucose, glycosylated hemoglobin, lipids, albumin, follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol) and urinary analysis (albumin, creatinine, and α-1-microglobulin) were obtained during complete or partial remission. Microalbuminuria was defined as urine albumin excretion between 20 and 300 mg/10 mmol creatinine in male patients and between 30 and 300 mg/10 mmol creatinine in female patients.

Short stature was defined as a height less than −2.5 SD compared with normal stature for age and gender in the Dutch population (7). Body mass index (BMI) was calculated as weight/(height)² (kg/m²). Weight excess was defined as a BMI >25 in men and >24 in women. Obesity was defined as a BMI >30 (8). Hypertension in adults was defined as a BP of >140/90 mmHg or taking medication for high BP (9).

For two patients who were younger than 18 yr, age-specific percentiles of BP were used (10). GFR was calculated as creatinine clearance by the Cockcroft-Gault formula and corrected for body surface area (11,12).

Treatment

At onset of NS, all patients were treated with prednisone 60 mg/m² per d for 6 to 8 wk and with prednisone 40 mg/m² per 2 d during the subsequent 4 to 6 wk. Relapses of NS were treated by prednisone 60 mg/m² per d until the disappearance of proteinuria followed by prednisone 40 mg/m² per 2 d for 4 wk. All patients received CP (2 to 3 mg/kg per d during 8 to 12 wk after renal biopsy confirming MCNS), but continued to relapse after CP course and were treated with CsA combined with steroids. The dosage of CsA was regularly adapted to maintain CsA trough levels between 100 and 150 ng/ml and was decreased in case of suspected toxicity, which was determined as 10% rise of serum creatinine between two outpatient visits. We attempted to decrease the dosage of prednisone to the lowest possible levels. In patients with relapsing disease during CsA treatment, further immunosuppressive therapy was determined individually as mentioned in Table 1.

Ophthalmologic Examination

All patients underwent a standardized ophthalmologic examination, including assessment of best corrected visual acuity, measurement of refraction, external inspection, measurement of intraocular pressures with applanation tonometry, anterior segment slit-lamp microscopy after mydriasis of the pupils, and direct and indirect ophthalmoscopy.

Dual-Energy X-Ray Absorptiometry Scan

All patients underwent bone densitometry measurement by dual-energy x-ray absorptiometry using a QDR 4500 densitometer (Hologic, Waltham, MA) as described previously (13). The T score is the bone mineral density (BMD) compared with young adults expressed in SD difference. T score between −1.0 and −2.5 was defined as osteopenia, and a T score of less than −2.5 was defined as osteoporosis (14).

Baseline and Laboratory Examinations, Bone Densitometry, and Ophthalmologic Examination

Semen Analysis

Fresh semen was obtained by masturbation from eight patients and was analyzed within 2 h. Concentration, motility, and morphology were noted, and World Health Organization criteria were used for the cutoff levels (15). The semen analysis was done once during this study and had no defined temporal relationship to the last cyclophosphamide medication.

Molecular Analysis

Genomic DNA was isolated from peripheral blood leukocytes, and coding sequences of individual genes were amplified by PCR using intronic primers flanking the exons. Fragments included both DNA sequences of the individual exons, the splice donor, and splice acceptor sites. Primer data are available on request. The following genes were screened: NPHS1 (accession no. AF190637-AF035835), NPHS2 (AJ279246-AJ279253), CD2AP (AF164377-NT 007592), and ACTN4 (NM. 004924.2). The obtained products were analyzed by double-stranded DNA sequencing on a 3130 XL Genetic Analyzer (PE Applied Biosystems, Foster City, CA). The genomic DNA from 50 healthy control subjects and database search were used to confirm new mutations and exclude polymorphisms.

Results

Of 65 adult patients with childhood-onset, frequently relapsing MCNS, we identified 19 (29%) with at least one relapse in adulthood. Clinical and laboratory data of 15 patients who agreed to participate in the study, the results of dual-energy x-ray absorptiometry scan, and molecular analysis are presented in Tables 1 and 2.

Clinical Characteristics of the Patients

The median follow-up period after the onset of NS was 24 yr (range 10 to 39 yr). The group consisted of 12 male and three female patients. The median age was 27.5 yr (range 17.2 to 43.9 yr). Median number of relapses after CP course was 18 (range 7 to 50). Median cumulative dosage of CP was 172 mg/kg (range 158 to 414 mg/kg). Five patients had one CP course, six patients had a second course, and three patients also had a third course. The cumulative dosage of steroids could not be calculated because dosages that were given for relapse treatment could not precisely be retrieved from the patient’s records. Twelve (80%) of 15 patients were still treated with immunosuppressive medication for preventing relapses of NS (Table 1).

BP was elevated in one of 15 patients, and six of 15 patients used antihypertensive medication (Table 1). Short stature was observed in three of 12 men. Female patients had a normal height according to the Dutch growth diagrams. In the male patients, we observed obesity in two and a decreased BMI (18.8 kg/m²) in one (Table 1). No correlation was found among height, BMI, and the number of relapses.

Laboratory Examinations, Bone Densitometry, and Ophthalmologic Examination

The GFR calculated by the Cockcroft-Gault formula and corrected for body surface area was normal in all patients. There were no cases of diabetes or hyperlipidemia.

Urinary examination showed microalbuminuria in three of 15 patients and albuminuria in four of 15 patients, whereas
<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at Onset of NS (yr)</th>
<th>Age at the Time of the Study (yr)</th>
<th>No. of Relapses after Last CP</th>
<th>Cumulative CP Dosage (mg/kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
<th>BP (mmHg)</th>
<th>Current Medications</th>
<th>Duration of CsA Therapy (mo)</th>
<th>Duration of Remission (mo)</th>
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<tr>
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<td>42</td>
<td>20</td>
<td>248</td>
<td>156.5</td>
<td>24.5</td>
<td>126/80</td>
<td>Pred, CsA, ena, Ca</td>
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</tr>
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<td>32</td>
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<td>19.8</td>
<td>125/80</td>
<td>CsA</td>
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<td>–</td>
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<td>CsA, Ca</td>
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<td>F</td>
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<td>18</td>
<td>16</td>
<td>150</td>
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<td>19.2</td>
<td>110/70</td>
<td>Pred, tacro, MMF, ena, vitamin D</td>
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<td>120/80</td>
<td>Pred, los</td>
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<td>F</td>
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<td>26</td>
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<td>Pred, CsA</td>
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</table>

Ca, calcium; ena, enalapril; los, losartan; MMF, mycophenolate mofetil; peri, perindopril; pred, prednisone; tacro, tacrolimus; tri, triamcinolone; vitD, vitamin D.
Table 2. Results of laboratory examinations, DEXA scan, and molecular analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>GFR per Cockcroft-Gault (ml/min per 1.73 m²)</th>
<th>Serum Examination</th>
<th>Urine Examination</th>
<th>DEXA Scan T Score</th>
<th>Mutation Analysis</th>
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<tr>
<td></td>
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<td></td>
<td>Albumin (g/L)</td>
<td>Cholesterol (mmol/L)</td>
<td>Albumin (mg/10 mmol Creatinine)</td>
<td>α-1-MG (mg/10 mmol Creatinine)</td>
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<td>40</td>
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<td>861.1</td>
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<td>123</td>
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<tr>
<td>11</td>
<td>M</td>
<td>105</td>
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<td>39</td>
<td>4.0</td>
<td>7.9</td>
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</table>

Reference values: >90 35 to 52 4.7 to 6.5 Male <20 Female <30

α-1-MG, α-1-microglobulin; DEXA, dual-energy x-ray absorptiometry; ho, homozygous; ND, not done.
serum albumin was normal in all patients. Two patients had increased excretion of α-1-microglobulin.

Osteoporosis was observed in three of eight male and one of three female patients. There was no correlation between bone mineral content (BMC) and BMI or height of the patients. Ophthalmologic examination revealed moderate myopia (spherical equivalent of refraction error (SE) of −1 to −5) in 10 of 15 patients; bilateral posterior subcapsular cataract (PSC) in three of 15 patients; and high hyperopia, strabismus, and amblyopia in one of 15 patients (Table 2).

**Fertility Examination**

All patients completed normal pubertal development and achieved Tanner stages G5P5 in male patients and M5P5 in female patients. Sperm analysis was performed 0 to 32 yr after the last CP treatment in eight male patients. Hormonal status was normal in all examined men and women.

The semen analysis showed oligozoospermia in one of eight male patients. Sperm motility was decreased in four of eight male patients, and six of eight patients had teratozoospermia. Patient 6 was still using CP at the time of sperm analysis and had normal sperm count and motility. Thus far, one male patient fathered a child and none of the three female patients has tried to get pregnant yet (Table 3).

**Molecular Analysis of NPHS1, NPHS2, CD2AP, and ACTN4**

Molecular analysis of podocyte genes demonstrated a heterozygous NPHS1 mutation (Pro264Arg) in three patients, described before in patients with congenital NS (16). The known NPHS1 Glu117Lys polymorphism was detected in a heterozygous state in eight patients and in a homozygous state in one patient (17). The NPHS2 Arg229Gln polymorphism was found heterozygously in two patients. There was no correlation between number of relapses and the presence of genetic abnormalities. No mutations or polymorphisms leading to an amino acid substitution were detected in CD2AP and ACTN4 genes.

**Discussion**

There are scarce data concerning the long-term outcome of children with MCNS. Two studies in the 1980s conducted in the pre-CsA era revealed a percentage of 5.5 and 26% of persistent relapses of biopsy-proven MCNS in adulthood (3,4).

Two more recent studies also included patients who were using calcineurin inhibitors. The first one by Fakhouri et al. (2) demonstrated that 42% (43 of 102 patients) of all patients with childhood MCNS had at least one relapse after puberty. Another study by Ruth et al. (18) found that 33% (14 of 42 patients) relapsed in adulthood. Our own recent survey showed that >25% of CP-treated patients with childhood onset of MCNS needed medical therapy in adulthood (19).

Of 78 patients who completed pubertal growth, described by Kyrieleis et al. (19), we examined 15 (19%) patients with relapsing course of NS after puberty and focused on long-term complications and possible underlying molecular defects. The patients were referred to our tertiary center for the evaluation of FRNS, and in all, the diagnosis of MCNS was proved by kidney biopsy; therefore, the described group is not representative of overall patients with idiopathic NS of childhood.

**Growth**

It is generally accepted that prolonged use of corticosteroids results in impaired growth (20,21). All of our patients developed NS at young age and were treated with corticosteroids for years. Three of 12 male patients had impaired growth, two of them were older than 30 yr, and growth impairment in these patients may represent that in the period of their growth, steroid-sparing agents were not yet introduced in the clinical practice. Growth impairment was not observed in three female patients; however, the low number of patients precludes any conclusion. Two men also had an increased BMI >30, indicating obesity.

**Treatment**

At the time of the study, only two of 15 patients did not receive any medications and were in a permanent remission of NS. Twelve patients were still using immunosuppressive medication, resulting in a complete or partial remission of NS. Thus, immunosuppressive treatment remained effective in these patients. One patient had elevated BP, and six patients were also on antihypertensive treatment, indicating that hypertension is a significant sequelae.

Table 3. Results of fertility examination in male patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Concentration (10^6/ml)</th>
<th>Motility (%)</th>
<th>Dysemorphic Head (%)</th>
<th>LH (E/L)</th>
<th>FSH (E/L)</th>
<th>Testosterone (nmol/L)</th>
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<tbody>
<tr>
<td>2</td>
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<td>93</td>
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<td>10.2</td>
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<td>3</td>
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</table>

Patient numbers in Table 3 correspond to the numbers in Tables 1 and 2. FSH, follicle-stimulating hormone; LH, luteinizing hormone.
frequent complication in this group of patients. In people of similar age, the prevalence of hypertension amounts to 5 to 10% (22). Admittedly, of this group of seven patients with hypertension, six were treated with a corticosteroid and/or calcineurin inhibitor, which may be the cause and/or may contribute to these individuals’ hypertension. This is in contrast with the data of Fakhouri et al. (2), who did not report hypertension in their patient population.

Renal Function Outcome and Comorbidity
As found in the other studies, renal function outcome was good in all patients: All of them had a normal creatinine clearance (2,18). Our strategy of decreasing calcineurin inhibitor dosage in case of serum creatinine elevation probably prevented overt renal toxicity. Because no sequential biopsies were performed, histologic signs of toxicity cannot be excluded. No patients had hyperlipidemia, diabetes, or malignancies. Early reviews reported few cases of malignancies after protracted courses of CP, but these patients were treated continuously with CP for up to 2 yr (3). Although the sample size of our study is small, these data support contention that the currently used dosage of CP is safe concerning malignancy potential (23).

Ocular Complications
Cataract and increased ocular pressure are recognized complications of prolonged steroid therapy (24). Typically, cataracts that are caused by steroids are PSCs, which occur within the visual axis and therefore substantially impair visual acuity (25). Possibly, steroids dysregulate proliferation and apoptosis of the lens epithelial cells (26,27) or can even directly bind to the lens proteins, resulting in changes of normal protein structure and lens opacities (28).

Hayasaka et al. (29) found in a group of 45 Japanese children with NS of various origin 33% with PSC. The maximum total duration of prednisone treatment in these patients was 11 yr. Nine of 45 children had a transient increase in ocular pressure during the steroid treatment, which normalized after cessation of the medication in all but one patient.

Another study by Ng et al. (30) examined 29 children with NS (73% with MCNS). In that study, 10% of the patients had bilateral PSC and 6.5% had marginally elevated intraocular pressure.

In our study population, three of 15 had bilateral PSC. The ocular pressure was normal in all patients at the time of examination. It is interesting that we observed a high prevalence of moderate myopia, which was found in 66% of patients. Myopia nowadays affects >30% of adults worldwide (31). Although the frequency in our patient group was twice as high, we cannot exclude a random effect. As far as we know, there are no reports on a deteriorative effect of immunosuppressive medications on ocular refraction; however, it would be important to study visual acuity and refraction in more detail in a larger population of patients who are treated for a long time with steroids, CsA, and CP. One might speculate that a transient elevation of intraocular pressure or changes of ion composition in the vitreous fluid as a result of the administration of loop diuretics could influence eye axial dimensions and refractory capacity.

Bone Mineral Density
Data concerning BMD in patients with steroid sensitive NS are conflicting. Gulati et al. (32) demonstrated a decreased BMC of the spine in a group of 100 children with NS in 61% of these patients. In contrast, Leonard and colleagues (33,34) could not show significant deficits in BMC in 60 children aged 9.0 ± 3.4 yr with glucocorticoid-sensitive NS, when correction was made for bone area, age, gender, race, and Tanner stage. Only one study dealt with adults who were treated for childhood NS: Hegarty et al. (35) found in 34 adults a significantly decreased distal radial trabecular volumetric BMD (mean T score −1.04). The authors suggested that their method is the only correct way to measure BMC in patients with abnormal body size, which is often the case in patients who have used corticosteroids (35). It is interesting that 33 of 34 of the patients in that study had no relapses of NS during adult life. In contrast, all of our 15 patients experienced relapsing disease in adulthood; therefore, the cumulative steroid dosage should be higher in our group compared with the group of Hegarty et al. This might also explain that one third of our patients had T scores of the lumbar spine lower than −2.5, indicating osteoporosis.

Fertility
In the study by Hsu et al. (36), sperm analysis in 16 patients with idiopathic NS, 3 to 8 yr after cytotoxic treatment, revealed azoospermia in three and oligozoospermia in seven. Six patients had normal sperm counts. The serum levels of luteinizing hormone and follicle-stimulating hormone were normal in most of these patients. There was no correlation between the cumulative dosage of CP and the degree of abnormal sperm counts; however, a meta-analysis of the risk for infertility after CP treatment defined a threshold dosage of 168 mg/kg (37). We diagnosed oligozoospermia in one patient, the sperm motility was decreased in four of eight patients, and the majority of patients had increased proportions of abnormal forms. The last has been described in several studies as concuring with reduced sperm counts (38). Six of eight patients received immunosuppressive treatment at the time of sperm analysis, which could influence the outcome. We did not find a correlation between the cumulative dosage of CP and the risk for sperm abnormalities. The results of sperm analysis were better than expected: Seven of eight patients should be able to father children according to semen quality. Female patients seem to have less risk for developing ovarian dysfunction after CP. In 12 women with NS treated by a short course of CP, no gonadal dysfunction was observed (39).

Molecular Genetics
Alterations in podocyte genes, involved in the pathogenesis of congenital or steroid-resistant NS, might predispose the development of MCNS. The most frequent genetic defects found in our patient group were heterozygous mutations or polymorphisms in the NPHS1 gene encoding nephrin. It is interesting that these genetic defects were different from those described.
by Lahdenkari et al. (40) in a Finnish group of patients with MCNS. The NPHS1 polymorphism Glu117Lys was previously described in association with decreased creatinine clearance in patients with IgA nephropathy (41). According to the literature, the allele frequency of this polymorphism is 36.7% in an ethnically matched control population (17). A similar allele frequency of 33.3% was found in our group of patients. The previously described polymorphism in NPHS2 (Arg229Gln), associated with increased risk for microalbuminuria (42), was detected on one allele of two patients with MCNS. Tsukaguchi et al. (43) described an allele frequency of 3.6% for this polymorphism. Because in vitro translated Arg229Gln podocin showed a decreased binding efficiency to nephrin, the possibility that NPHS2 Arg229Gln enhances susceptibility to FSGS in association with a second mutant NPHS2 allele is suggested (43). In our study population, the allele frequency for NPHS2 Arg229Gln was only slightly higher (6.7%). Because of comparable frequency of genetic alterations in NPHS1 and NPHS2 genes between our patient group and a healthy population, it seems unlikely that these defects make podocytes more susceptible to nephrotic insults.

Conclusions
At least one quarter of patients with biopsy-proven childhood-onset frequently relapsing MCNS will continue to relapse after puberty and require prolonged medical therapy. Although these patients maintain normal GFR, they frequently develop extrarenal complications such as osteoporosis, hypertension, and decreased visual acuity as a result of cataracts and myopia. One third of male patients who are treated with CP demonstrate decreased sperm count and motility. These findings indicated that new, more effective, and less toxic therapies should be sought for relapsing MCNS.

Disclosures
None.

References


Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/
CHILDHOOD KIDNEY DISORDER HAS LASTING EFFECTS

Minimal Change Nephrotic Syndrome Can Cause Osteoporosis, Hypertension, Cataracts, and Sperm Abnormalities

Washington, DC (September 22, 2009) — A kidney condition that can arise in children and was until recently believed to disappear after puberty may persist into adulthood and cause significant long-term complications, according to a study appearing in an upcoming issue of the Clinical Journal of the American Society Nephrology (CJASN). The findings indicate that better treatment options are needed for children with the disorder, called minimal change nephrotic syndrome.

Many children who develop minimal change nephrotic syndrome—a disorder that largely affects the blood filtering structures of the kidneys—can be successfully treated with prednisone. The cause of the syndrome is unknown but may be related to an autoimmune illness. Unfortunately, 10% to 40% of patients suffer relapses after childhood and must be treated long-term with immunosuppressive drugs.

To determine the lasting health effects of minimal change nephrotic syndrome and its treatment in patients who are not cured during childhood, Henriette Kyreileis, MD, PhD (Radboud University Nijmegen Medical Centre, The Netherlands) and Elena Levtchenko, MD, PhD (University Hospitals, Leuven, Belgium), and their colleagues studied 15 adult patients with the disease. The investigators ran a number of tests on the patients—including blood and urine analyses; semen analyses in men; x-ray exams; eye exams; and genetic tests.

Hypertension was found in 7 of the 15 patients, and osteoporosis was present in five of the patients. Eye exams revealed nearsightedness in 10 of the patients and cataracts in three of the patients. In the eight male participants in the study, low sperm count was found in one patient, reduced sperm motility was detected in four patients, and defective sperm were present in six patients.

The analysis revealed that while adults being treated for minimal change nephrotic syndrome may maintain normal kidney function, they frequently experience other serious health problems. Long-term immunosuppressive treatments may be the cause and/or may contribute to the development of these adverse

MORE
effects. “Our study underscores a need for more effective and less toxic therapies for relapsing minimal change nephrotic syndrome,” the authors wrote.

The authors report no financial disclosures. Study co-authors include Marije Löwik, Ing, Isle Pronk, Ing, Jan Kremer, MD, PhD, Wim Oyen, MD, PhD, Lambertus van den Heuvel, PhD, Johannes Cruysberg, MD, PhD, and Jack Wetzels, MD, PhD (Radboud University Nijmegen Medical Centre, The Netherlands).

The article, entitled “Long-Term Outcome of Biopsy-Proven, Frequently Relapsing Minimal-Change Nephrotic Syndrome in Children,” will appear online at http://cjasn.asnjournals.org/ on September 24, 2009, doi 10.2215/CJN.05691108.

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