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CLINICAL STUDY

Renal biopsy in children with steroid-dependent nephrotic syndrome

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Abstract: *Background:* There is lack of consensus on the necessity of renal biopsy in children with steroid-dependent nephrotic syndrome (SDNS) prior to cytotoxic therapy.
Objectives: To retrospectively evaluate: (a) the benefit of renal biopsy (RB) prior to cyclophosphamide therapy; (b) relationship between histopathologic results of RB samples and clinical course in children with SDNS.
Patients, materials and methods: RB was performed in 18 SDNS patients (11 boys and 7 girls). The mean age of the children at the time of nephrotic syndrome (NS) diagnosis was 6.4±3.9 years and 9.7±4.3 years at the time of RB. Following the RB, all children received prednisone and cyclophosphamide treatment for 12 weeks. Duration of remission and relapse rate was recorded.
Results: The histologic evaluation revealed minimal change disease (MCD; n=14) and IgM nephropathy (n=4). These results didn't affect the ongoing therapy. MCD patients had longer remission compared to IgM nephropathy (3.2±1.5 vs 1.7±0.8 years; p=0.05). Relapse rate did not differ significantly between MCD and IgM nephropathy (p=0.22). The duration of remission was inversely correlated to relapse rate after the treatment (r=-0.66, p=0.01).
Conclusion: We suggest that RB prior to cyclophosphamide therapy is not necessary in patients with SDNS *(Tab. 2, Ref. 14)*. Full Text (Free, PDF) *www.bmj.sk*.
Key words: steroid-sensitive nephrotic syndrome, renal biopsy, cyclophosphamide.

Nephrotic syndrome (NS) is characterized by protein leakage from the blood to the urine through the glomeruli resulting in proteinuria (960 mg/m^2/24 hours; i.e. >40 mg/m^2 per hour), hypoalbuminemia (serum albumin <25 g/L), hypercholesterolemia and generalised oedema (1–5). NS has an incidence of two to seven cases per 100,000 children per year, with a prevalence of 16 cases per 100,000 children (5). The most common histological findings include minimal change disease (MCD), diffuse mesangial hypercellularity (MH), and focal segmental glomerulosclerosis (FSGS), with FSGS having the worst long-term prognosis. Immunoglobulin M (IgM) nephropathy, characterised by glomerulonefritis with heavy proteinuria, diffuse granular mesangial IgM immunofluorescent deposits and electron-dense mesangial deposits, has been also found in NS. Some investigators suggest that IgM nephropathy is a clinically distinct entity with others stating that IgM nephropathy is a transitional state between MCD and FSGS (5). Children with idiopathic NS not having hematuria, hypertension, or impaired renal function are treated with corticosteroids without requiring a kidney biopsy. The standard medication for treatment is prednisolone or prednisone, the duration of initial therapy should be for a minimum of 12 weeks, with daily prednisone 60 mg/m^2 of body surface (2 mg/kg per day) divided into 3 doses/day for 6 weeks, followed by 40 mg/m^2 (1.5 mg/kg) as a single morning dose on alternate days for the next 6 weeks (1–3). However, about 70 % of children experience a relapsing course with recurrent episodes of oedema and proteinuria and often become steroid-dependent and exposed to long-term steroid complications (1–4). Relapse is defined as proteinuria exceeding 960 mg/m^2/24 hours for 3 consecutive days, whilst steroid-dependent nephrotic syndrome (SDNS) is defined as two consecutive relapses of NS in the course of alternate-day prednisone therapy or relapse within 14 days after the cessation of prednisone treatment (1, 2). The therapy of SDNS rests in the prolonged administration of corticosteroids, alkylating agents (cyclophosphamide, chlorambucil), levamizole, mycophenolate mofetil or calcineurin inhibitors (cyclosporin A, tacrolimus) (1, 2, 4–10). RB should be performed before therapy with calcineurin inhibitors (2) and has been considered as not necessary in patients with frequent relapses or steroid dependence before starting treatment with levamisole, cyclophosphamide, or MMF (2, 7–14), but there is no clear consensus. Our objective was to retrospectively evaluate: (a) the benefit of RB prior to cyclophosphamide therapy in children with SDNS, i.e. the effect of histological outcome of RB on physician's thera-

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Tab. 1. Patient data.

Parameter	Mean value±SD	Range
Age at the NS onset (years)	6.4±3.9	1.6–13.7
Age at RB (years)	9.7±4.3	2.8–17.0
Number of relapses between NS onset and RB	4.6±2.3	2–10

NS – nephrotic syndrome, RB – renal biopsy

peutic strategy; (b) relationship between histopathologic results of RB samples and clinical course in children with SDNS.

Patients and methods

Hospital charts of 18 children (11 boys and 7 girls) with SDNS were reviewed retrospectively. The mean age of the children at the time of the NS onset was 6.4±3.9 years (Tab. 1). All patients had oedema, proteinuria (960 mg/m^2/24 hours), hypoalbuminemia (serum albumin <25 g/L), normal C3 complement serum levels, normal glomerular filtration rate as determined by creatinine clearance, absence of macroscopic hematuria, no permanent hypertension, no signs of systemic disease. The clinical symptoms and laboratory results were characteristic of MCD. RB was performed at the mean age of 9.74.3 years; prior to RB, the patients suffered from 4.6±2.3 relapses (Tab. 1). Informed consent was obtained from each parent/guardian (and patient if applicable) prior to any diagnostic or therapeutic procedure. Renal biopsies were performed under either local (in children over 12 years of age) or general anaesthesia and under ultrasound guidance. All bioptic samples were representative (>10 glomeruli/ /tissue sample) and evaluated by an experienced nephropathologist. Following the RB, all patients were treated with prednisone (0.3–0.5 mg/kg/day) and cyclophosphamide (dose 2 mg/ /kg/day) for 12 weeks. The following was recorded: (i) impact of histopathologic finding on the physician's decision to change the therapeutic regimen, (ii) the duration of NS remission and number of relapses after the cyclophosphamide-prednisone treatment. Student's t-test and linear regression were calculated where applicable.

Results

The histologic evaluation of biopsy samples revealed MCD (n=14) and IgM nephropathy (n=4). In none of the patients were the results of histopathologic findings reason for whatever change in ongoing therapy with cyclophosphamide and prednisone.

After the treatment, 13 patients (MCD, n=10; IgM nephropathy, n=3) remained within remission lasting for more than one year, 2 patients (MCD) had sporadic relapse, while 3 patients (MCD, n=2; IgM nephropathy, n=1) relapsed and became steroid-dependent again.

Patients with MCD had longer remission compared with IgM nephropathy patients (Tab. 2). Number of relapses did not differ significantly between MCD and IgM nephropathy (Tab. 2).

Tab. 2. Duration of remission and number of relapses after the cyclophosphamide treatment.

Parameter	Mean±SD	Range
Remission in MCD (years)	3.2±1.5^{+}	0.1–5.0
Remission in IgM (years)	1.7±0.9^{+}	0.6–2.8
Number of relapses in MCD	1.0±1.9^{++}	0–5
Number of relapses in IgM	2.5±2.5^{++}	0–6

$^{+}$– p=0.05 duration of remission between MCD and IgM nephropathy, $^{++}$– p=0.22 number of relapses between MCD and IgM nephropathy, MCD – minimal change disease

The duration of remission was inversely correlated to number of relapses after the cyclophosphamide treatment (r=-0.66, p=0.01) either in children with MCD or in pooled data (MCD plus IgM nephropathy).

Discussion and conclusions

The results of histopathological findings confirmed the predominance of MCD in patients with SDNS (5, 8, 10). These results did not affect the therapeutic strategy in our SDNS paediatric patients, with cyclophosphamide being administered for 12 weeks. Such findings are fully in accordance with previous studies involving 148 children with SDNS and questioning the benefit of renal biopsy prior to cytotoxic therapy (2, 8, 11–14). MCD patients had longer remission compared to patients with IgM nephropathy. This might be due to the fact that IgM nephropathy has been shown to have a significantly poorer response to steroids and immunosuppressive agents than MCD (5). As expected, the duration of remission was inversely correlated to number of relapses, supporting previous observation of lower relapse rate and longer relapse free period after cyclophosphamide treatment (6, 9, 10). Our findings further support the clinical impression that steroid sensitivity rather than histology is the major determinant of prognosis in childhood nephrotic syndrome (11). In conclusion, we support the decision that renal biopsy prior to cyclophosphamide treatment is not obligatory in patients with steroid-dependent NS and that therapy with alkylating agent can be initiated without previous renal biopsy.

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