Eur J Pediatr (2006) 165:839–844
DOI 10.1007/s00431-006-0177-1

ORIGINAL PAPER

Expression of P-glycoprotein in lymphocytes of children with nephrotic syndrome treated with glucocorticoids

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Received: 1 March 2006 / Accepted: 2 May 2006 / Published online: 1 June 2006

Abstract
Introduction Glucocorticoids are still the mainstay of therapy for nephrotic syndrome (NS) in children. Poor response to glucocorticoids may relate, in part, to the overexpression of P-glycoprotein (P-gp). The aim of the present study was to determine the expression of P-gp in lymphocytes (CD3) in the peripheral blood of children with steroid-sensitive nephrotic syndrome in the dynamics of the disease. The study group (I) consisted of 18 children, median age 5.75 years, with steroid-sensitive nephrotic syndrome, in whom the examinations were carried out three times: (A) before treatment, during relapse; (B) after 3–4 weeks of prednisone treatment; (C) 2 months after finishing prednisone treatment. The control group (II) consisted of 18 healthy children of the same age. P-gp expression in CD3 lymphocytes of peripheral blood was measured using flow cytometry. During NS relapse and prior to glucocorticoid administration, the CD3/P-gp level was higher (median 3.20%, range 0.80–7.80%) when compared to healthy controls (1.10%, range 0.30– 2.20%) ($p<0.01$). During glucocorticoid treatment, CD3/P-gp increased significantly and was much higher than in the control group ($p<0.01$) and in the NS children before treatment ($p<0.01$). In remission, the P-gp expression decreased, but did not achieve the values of the controls ($p<0.05$). Fourteen out of eighteen (14/18) children still showed P-gp values above the cut-off level. We also found a positive correlation between the P-gp expression and total prednisone dose in the NS children in all examinations: A: ($r=0.540$, $p<0.05$); B: ($r=0.630$, $p<0.01$); C: ($r=0.653$, $p<0.01$).
Conclusion In conclusion, the overexpression of P-gp in remission, after finishing glucocorticoid treatment, may indicate that P-gp plays a role in the response to corticosteroids in nephrotic children.

Keywords Children · Glucocorticoids · Nephrotic syndrome · P-glycoprotein

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Introduction

The term "nephrotic syndrome" (NS) describes the clinical state characterised by the presence of proteinuria and hypoalbuminaemia, leading to edema and hypercholesterolaemia. In contrast to adults, most children with NS have idiopathic nephrotic syndrome. The most common forms of idiopathic NS in children are minimal change NS (MCNS) and focal segmental glomerulosclerosis (FSGS).

Corticosteroids have been the mainstay of therapy for NS for nearly 50 years. The International Study of Kidney Disease in Children (ISKDC) established the standard initial treatment of idiopathic NS as 4 weeks of daily steroids [19]. Those patients who go into remission with steroid therapy alone are called steroid-responsive, whereas those patients in whom remission is not achieved after 8 weeks of steroid therapy are labelled steroid-resistant [3]. The idiopathic NS of childhood is characterised by steroid-responsiveness in over 90% of cases [19]. Despite response

to corticosteroids, up to 60% of patients with steroid-sensitive NS develop a frequently relapsing or steroid-dependent course [6]. Children with frequent relapsing or steroid-dependent NS undergoing long-term and repeated treatment with glucocorticoids are at risk of adverse drug effects, in particular, growth retardation and obesity [1].

Glucocorticoids block the effect of inflammatory cytokines by entering the cell and binding to the intracellular glucocorticoid receptor. Within the cell, cortisol acts in three ways. First, the cortisol-glucocorticoid receptor moves to the nucleus, where it binds to glucocorticoid-responsive elements [10]. Second, regulation of other glucocorticoid-responsive genes involves interaction between the cortisol-glucocorticoid receptor complex and other transcription factors, such as nuclear factor-κB complex [16]. The third mechanism is glucocorticoid signalling through membrane-associated receptors. It is so called non-genomic pathways [9].

It was previously thought that the transport of glucocorticoids into and out of the cell is a simple diffusion only, but Meijer et al. [17] showed that the penetration of dexamethasone into the brain is limited by the presence of the multidrug resistance gene (MDR1). Also, in vitro studies show active transport of glucocorticoids out of high MDR-expressing cells, with significant reduction of their intracellular concentration [2, 22].

P-glycoprotein (P-gp), encoded by MDR1, is a transmembrane efflux pump that is widely expressed on various tissues, including the blood–brain barrier, liver, kidney, intestine and peripheral blood lymphocytes [8, 23]. Because P-gp is expressed on T-lymphocytes, it could affect immune responsiveness and pharmacological response to many drugs. P-gp is involved in the transport of cytokines such as Il-2 and INF-gamma in peripheral lymphocytes, which play an important role in the pathogenesis of NS [5]. However the role of P-gp on these cell populations is still unknown.

Overexpression of P-gp results in the reduction of the intracellular concentration of xenobiotics, drugs and poisons, such as vinca alkaloids, anthracyclines, verapamil, colchicines, antimalarials, cyclosporine A and corticosteroids [2, 20–22]. Thus, P-gp seems to be involved in both protecting cells from these drugs and in developing resistance to them.

The aim of the present study was to determine the expression of P-gp in CD3 lymphocytes in the peripheral blood of children with steroid-sensitive nephrotic syndrome, in the dynamics of the disease, using flow cytometry.

Subjects and methods

The examinations were performed on two groups of children. The study group (I) consisted of 18 children (10 female, 8 male), median age 5.75 years with steroid-sensitive nephrotic syndrome, in whom the examinations were carried out three times: (A) before treatment, during relapse (proteinuria>50 mg/kg b.w./24 hours, concentration of albumin< 25 g/L, generalised oedema); (B) after 3–4 weeks of prednisone treatment with dose 60 mg/m^2; (C) 2 months after finishing prednisone treatment, in total NS remission. In 6/18 children, it was the first episode of NS, the rest (12/18) of the NS children were in consecutive (1–3) relapse of NS, but they had been in remission for at least 12 months. Age at onset was of median 4.40 years (range 2.10–14.2 years), the mean ratio of NS relapses was median 2.0 (range 0.0–3.0). In all of the sick children, regression of the symptoms was observed after 1–3 weeks of treatment.

The control group (II) consisted of 18 healthy children (10 female, 8 male), median age 6.50 years (range 2–17 years), never treated with glucocorticoids. None of the children had any other systemic disorders.

Methods

We measured P-gp expression on peripheral blood lymphocytes T (CD3) of patients with NS using a flow cytometry assay. P-gp expression was quantified by the percentage of P-gp positive cells and the absolute number of cells per μl. Double (FITC/PE) monoclonal antibodies for immunophenotyping analysis were purchased from Becton, Dickinson and Company. All other reagents were obtained from Coulter. Flow cytometric analysis was performed by Coulter Epics XL in whole blood procedure.

The study was approved by the ethics committee of the Medical Academy in Białystok in accordance with the Declaration of Helsinki.

Data analysis was performed using the software package Statistica 6.0. Since no features of normal disintegration were found in the groups examined with the Shapiro-Wilk test, statistical analysis was performed using the non-parametric Mann-Whitney U test or the Wilcoxon test. Spearman correlation coefficients were calculated for statistically significant correlations. Multivariate analysis was done by stepwise logistic regression analysis. A p value of less than 0.05 was considered to be statistically significant.

Results

The characteristics of the patients with NS and the control population are summarised in Table 1.

In both groups, the children were of similar age and sex. In 6/18 NS children, it was the first episode of illness; in 2/18 cases, it was the first relapse and in 5/18, the second and in the same number the third.

Renal biopsy was performed in 10/18 patients with relapses of NS. In the remaining two cases with NS

Table 1 Characteristics of the study subjects

		Nephrotic patients (I) (n=18) Median (range)	Healthy controls (II) (n=18)
Age (years)		5.75 (2.0–17.0)	6.50 (2.0–17.0)
Sex (F/M)		10/8	10/8
Age at onset (years)		4.40 (2.10–14.2)	–
Number of NS attacks		2.0 (0.0–3.0)	–
Renal biopsy		10/18	
Histopatological findings	MCNS	8/10	
	Early FSGS	2/10	
Cumulative dose of prednisone (mg/kg b.w.)		326.0 (0.0–610.0)	

relapses, renal biopsy was not performed. Minimal change nephrotic syndrome (MCNS) was the most common histopathological lesions (8/10), followed by early FSGS. At the beginning of the first examination, all of the children were in remission (albumin/creatinine ratio<0.1). The cumulative dose of steroids in NS children in examination A was median 326.0 mg/kg b.w (range 0.0–610.0 mg/kg b.w).

The percentage of total lymphocytes of the peripheral blood and their absolute number in children with the nephrotic syndrome before treatment (IA) did not differ from the healthy controls (II), but it decreased during glucocorticoid treatment in examination (B), although the difference was not statistically significant (p>0.05). In complete remission of NS, after at least a 8-week period free of steroids, the number of lymphocytes increased and was similar to the initial values and the difference was not statistically significant (p>0.05).

The percentage of CD3 lymphocytes and their absolute values also decreased significantly during treatment with glucocorticoids.

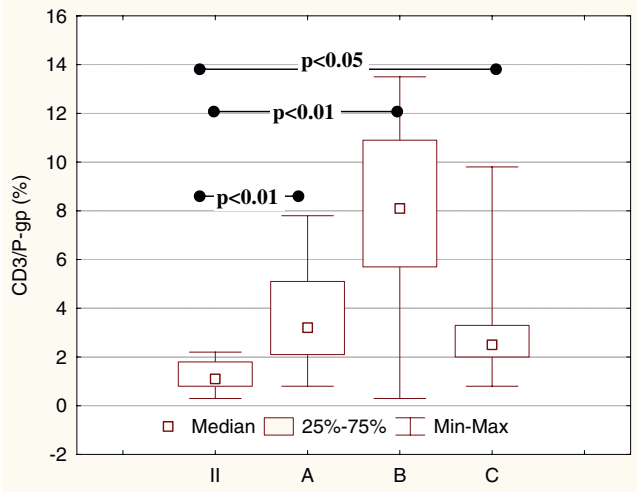

Fig. 1 P-glycoprotein (P-gp) expression in CD3 lymphocytes of children with nephrotic syndrome (NS, I) in the dynamics of disease (A, B, C) and in the control group (II)

We evaluated the expression of P-gp on CD3 lymphocytes from children with NS before (A), during (B) and after glucocorticoid treatment (C) (Fig. 1). Prior to glucocorticoid administration, during NS relapse, the expression of P-gp in the CD3 lymphocytes (CD3/P-gp) was higher (median 3.20%, range 0.80–7.80%) when compared to healthy controls (median 1.10%, range 0.30–2.20%) (Table 2).

The absolute number of CD3/P-gp in NS children was almost three times higher when compared to healthy controls (p<0.01). The absolute number of P-gp in cells other than CD3 cells was also higher than in the control group (p<0.01).

When P-gp expression was compared according to the number of NS attacks in steroid-sensitive children, we found that, in children with first attack, the expression of P-gp in CD3 lymphocytes was 1.66% (range 0.8–2.3%) and did not differ from healthy controls, while in children with first–third relapse, the expression of P-gp was much higher 4.33% (range 1.75–6.68%) (p<0.01). During glucocorticoid treatment, after 3–4 weeks of prednisone at a dose 2 mg/kg b.w., the expression of P-gp was much higher than in the control group (p<0.01) and in the NS children before treatment (p<0.01).

We also checked what the expression of P-gp in the CD3 lymphocytes of peripheral blood is 8 weeks after finishing the glucocorticoid therapy. We found that the P-gp expression decreased, but was still much higher than in healthy controls (p<0.05).

We also analysed the expression of P-gp on CD3 lymphocytes from the particular NS children before (A), during (B) and after (C) glucocorticoid therapy (Fig. 2). Prior to administration of prednisone, the expression of CD3/P-gp was above the cut-off in 11/18 of NS children, mainly with first–third relapse of NS. After 3–4 weeks of prednisone treatment, we found that, in the majority of patients, the P-gp expression increased and was significantly higher than before treatment (Wilcoxon rank p<0.01). In examination C after finishing prednisone therapy, CD3/P-gp decreased in all of the patients but, interestingly, 14 of the 18 patients still showed P-gp values above the cut-off level.

Table 2 Lymphocytes, CD3 lymphocytes and P-gp in children with the NS (median and ranges) (I) before treatment (A), after 3–4 weeks of treatment (B) and in remission (C), and in the control group (II)

Group		*n*	Total lymph (%)	Total lymph/μl×10^3 (a.n.)	CD3 (%)	CD3/μl (a.n.)
II		18	30.8 (11.8–47.6)	2.020 (1.140–3.960)	66.0 (41.9–72.3)	1260 (752.0–2037.0)
I	A	18	32.4 (9.7–53.4)	2.030 (0.370–4.660)	67.25 (38.1–81.9	1382.2 (169.8–2970)
	B	18	29.4 (9.7–45.6)	1.790 (0.370–3.290)	62.7 (40.90–73.7)	1132.2 (169.8–2011)
	C	18	33.6 (19.7–52.7)	1.890 (0.990–3.930)	61.85 (30.5–74.0)	1118 (638.5–2758.8)
Group		*n*	CD3/P-gp (%)	CD3/P-gp (a.n.)	Total P-gp (%)	Total P-gp (a.n.)
II		18	1.10 (0.30–2.20)	17.2 (2.49–29.06)	3.25 (1.8–5.3)	70.0 (14.0–100.0)
I	A	18	3.20 (0.80–7.80)**	32.8 (6.01–168.3)**	6.70 (1.8–91.0)**	77.55 (14.0–324.0)
	B	18	8.10 (0.3–13.50)**	85.82 (2.49–217.9)**	13.60 (5.0–34.5)**	172.5 (19.0–908.0)**
	C	18	2.50 (0.80–9.80) *	29.10 (9.54–94.02)*	5.85 (3.0–20.5)*	86.0 (30.0–175.0)

a.n.=absolute number; *p* comparison with healthy controls: *$p<0.05$, **$p<0.01$

When analysing the correlation between P-gp expression in lymphocytes (CD3/P-gp) and total prednisone dose in children with NS, a positive correlation between the P-gp expression and the total prednisone dose in NS children appeared in all subgroups: A: ($r=0.540$, $p<0.05$); B: ($r=0.630$, $p<0.01$); C: ($r=0.653$, $p<0.01$).

Multiple regression analysis showed no significant association between the P-gp expression and age, sex, disease duration, activity, assessment by urinary protein loss and serum albumin concentration.

Discussion

Corticosteroid treatment in patients with nephrotic syndrome (NS), a disease characterised by the activation of T-cells, is used to suppress highly activated lymphocytes. Although most nephrotic patients seem to be quite homogeneous in terms of biochemical alterations and clinical manifestations, substantial differences are encountered regarding the course of disease. Approximately 60% to 80% of steroid-sensitive nephrotic syndrome patients experience relapses of proteinuria and some remain steroid-dependent or become steroid-resistant, despite initial complete remission [11]. Several mechanisms for the lack of response to corticosteroids have been considered. This may be ascribed to overwhelming disease severity, poor compliance, abnormalities in glucocorticoid metabolism or poor absorption, especially in patients with NS, who often develop heavy proteinuria and Hypoalbuminaemia, and, finally, by glucocorticoid resistance due to a glucocorticoid receptor or postreceptor abnormality. The role of glucocorticoid receptors in worsening the response to steroids was described earlier by our group [24, 25], but the clinicians often meet with a number of patients not adequately responding to these agents, either due to inherited target tissue defective response or acquired impaired responsiveness. Recent investigations brought much insight into the molecular mechanisms of glucocorticoid resistance. Much data indicate that poor response to glucocorticoids may relate, in part, to overexpression of P-glycoprotein (P-gp).

The study of drug resistance mechanism, particularly multidrug resistance gene (MDR1), is not only described in neoplastic diseases. Research on the MDR1 phenotype in autoimmune disorders, particularly in rheumatoid arthritis (RA) patients, began in the mid-1990s. Jorgensen et al. [12] described high P-gp messenger ribonucleic acid (mRNA) levels in synovium from RA patients treated with three immunosuppressive drugs. Maillefert et al. [15] found P-gp surface overexpression in peripheral lymphocytes from RA patients under long-term steroid therapy. The overexpression of P-gp in immune cells may be associated with an increased efflux of steroids and, consequently, with an insufficient therapeutic effect. Other investigators have reported that decreased cytoplasmatic glucocorticoid concentrations are the result of an increased P-gp-mediated efflux of glucocorticoid from lymphocytes and is one of the mechanisms of glucocorticoid resistance in asthma and inflammatory bowel diseases [7, 18]. The role of P-gp was also described in other diseases like HIV infection, inflammatory bowel diseases, as well as in autoimmune disorders, such as systemic lupus erythematosus and immune thrombocytopenic purpura [4, 7, 13, 14].

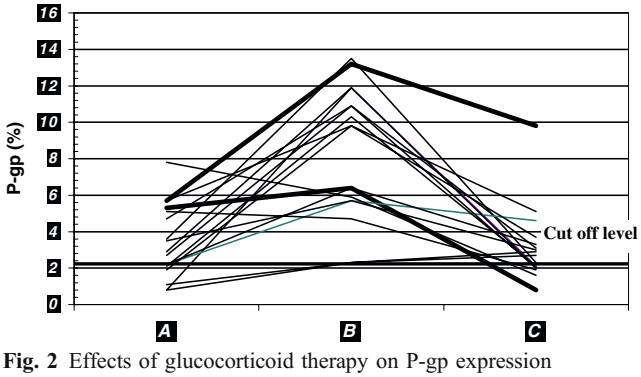

Fig. 2 Effects of glucocorticoid therapy on P-gp expression

The major findings in this study were significantly elevated P-gp expression in CD3 lymphocytes of NS children during prednisone treatment in all steroid-sensitive children. Interestingly, NS patients under prednisone therapy, independently of their clinical status, exhibited higher P-gp expression in lymphocytes than in remission without prednisone, suggesting that the P-gp function might be induced by the treatment itself. Since one of the main physiological function of P-gp is detoxification, it is possible that its activity may be a result of high prednisone dosage. It was also confirmed by positive correlation between the P-gp expression and the total prednisone dose in NS children in all examinations (A–C).

The expression of P-gp was dependent on the number of NS attacks. In children with the first attack of NS, the expression of Pg-P in CD3 lymphocytes was median 1.66% (range 0.8–2.3%) and did not differ from healthy controls, while in children with consecutive attacks, in spite of at least a 12-month remission without steroids, the expression of P-gp was much higher, median 4.33% (range 1.75–6.68%) ($p<0.01$).

We also demonstrated that high levels of P-gp expression in NS patients is still increased after two months without steroid treatment. Different results were shown by Diaz-Borjon et al. [4] in patients with lupus erythematosus. The authors showed no differences in patients in clinical remission when compared to controls, while the active group exhibited the highest P-gp values.

It is possible that P-gp is a factor which captures drugs when they pass through the cell membrane and then releases them outside the cell. When the number of P-gp molecules expressed on lymphocytes is high, corticosteroids, which are the substrate of P-gp, are not able to reach the cytoplasm. In this situation, the responsiveness to steroids becomes worse. In clinical practise, it is often observed that frequent relapsers do not response to steroids as well as they did at the beginning of treatment. In our study, we assessed P-gp expression in a group of steroid-sensitive nephrotic children and the influence of steroid treatment on P-gp expression during 6 months of treatment and observation. We found that a two-month period without glucocorticoid treatment is not enough to decrease the P-gp expression to baseline values. Interestingly, 14 of the 18 patients still showed P-gp values above the cut-off level. This may be one the reasons for the worse steroid responsiveness in the refractory group.

In conclusion, we demonstrated that the expression of P-gp in CD3 lymphocytes is changing during the course of glucocorticoid treatment. Overexpression of P-gp in remission after the finishing of the glucocorticoid treatment may indicate that P-gp may play some role in the response to corticosteroids in nephrotic children.

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