Pediatr Neonatol 2010;51(3):166–171

ORIGINAL ARTICLE

Evaluation of Right Ventricle Function in Children With Primary Nephrotic Syndrome

Qiang Qin*, Ruiying Xu, Junhua Dong, Wei Xia, Ruopeng Sun

Department of Pediatrics, Qilu Hospital of Shandong University, Jinan, China

Received: Jan 8, 2009
Revised: Sep 1, 2009
Accepted: Sep 21, 2009

KEY WORDS:
cardiovascular;
cytokines;
Doppler echocardiography;
primary nephrotic syndrome;
right ventricle function

Background: We aimed to evaluate right ventricle (RV) function in children with primary nephrotic syndrome (PNS).
Methods: RV hemodynamics were evaluated by Doppler echocardiography in 50 children with PNS (aged 2.5–12 years), either at PNS onset ($n=37$) or relapse ($n=13$), and in 50 normal controls. Heart rate, stroke volume, cardiac output, RV end-diastolic and end-systolic volume, RV ejection fraction, RV end-diastolic pressure, RV peak systolic and end-systolic pressure were determined from pressure-volume loops. The maximal rates of RV pressure upstroke and fall (dP/dt_{max} and dP/dt_{min}, respectively) were calculated. Effective pulmonary arterial elastance was calculated as end-systolic pressure divided by stroke volume. Plasma tumor necrosis factor-α (TNF-α) and insulin-like growth factor 1 (IGF-1) were also measured.
Results: RV end-diastolic pressure was increased by an average of 20% in 39 of the patients with PNS, whereas RV ejection fraction was reduced by an average of 15% compared with controls ($p<0.05$ for both). Cardiac output and stroke volume were maintained, indicating compensation at the expense of increased RV end-diastolic and end-systolic volumes and increased RV filling pressure ($p<0.05$). Plasma TNF-α was elevated in patients with PNS (326 ± 117 kU/L *vs.* 75 ± 23 kU/L, $p<0.05$); IGF-1 was similar in PNS patients and controls.
Conclusion: Right ventricle function was impaired in children with PNS. The characteristics were unrelated to blood pressure and IGF-1, but may be correlated with TNF-α and disease duration. Further studies are needed to evaluate the etiology and clinical implications of this abnormality.

1. Introduction

There is an increased incidence of heart disease in patients with chronic primary nephrotic syndrome (PNS), which may be attributable to the malnutrition and activated inflammatory state associated with the sustained proteinuria. PNS is also associated with hypercoagulability and an increased tendency for thromboembolism.[1,2] The reported incidence of thromboembolic complications ranged from 1.8% to 6.6% in children with PNS.[1,2] Although thromboembolism may occur anywhere, deep vein thrombosis and pulmonary embolism are the most frequently encountered manifestations in the clinical setting, and may be correlated with right ventricle (RV) function. Another report[3] has suggested

*Corresponding author. Department of Pediatrics, Qilu Hospital of Shandong University, 107 Wenhua Road West, Jinan 250012, China.
E-mail: qin-qiang@126.com

that a higher frequency of serious cardiac complications, particularly cardiomyopathy and congestive heart failure, occur in children with focal segmental glomerulosclerosis (FSGS). The authors speculated that the immune mechanism responsible for the development of FSGS may also affect the heart.[3] Gerald et al[4] studied the vascular function of the peripheral circulation in patients with nephrosis, and suggested that patients with nephrosis had abnormal endothelium-dependent but preserved endothelium-independent dilation of the brachial artery following an ischemic stimulus. Dyslipoproteinemia is probably responsible for endothelial dysfunction in the conduit arteries in patients with nephrosis, and could form the basis for the increased risk of cardiovascular disease in these patients.[4]

In this study, we evaluated RV function in children with PNS using Doppler echocardiography. We suggest that protein wasting and systemic inflammatory activation during PNS may contribute to cardiac remodeling and dysfunction.

2. Methods

2.1. Subjects

Fifty consecutive children (36 males, 14 females) with PNS at onset or relapse admitted to our nephrology unit were prospectively studied from January 2002 to January 2004. The age range was 2.5–12 years (mean ± SD, 6.6 ± 3.4 years). PNS was defined by heavy proteinuria (urinary protein > 1 g/m^2/day), hypoalbuminemia [serum albumin < 2.5 g/dL (25 g/L)], hypercholesterolemia and edema.[5] The initial treatment comprised 2 mg/kg/day (maximum 60 mg/day) of prednisone given orally in three divided doses for 4 weeks, followed by therapy on alternate days for another 4 weeks. The daily dose was then tapered for 4–6 weeks and finally stopped. Response was defined as disappearance of proteinuria (< 4 mg/m^2/day on 3 consecutive days). Patients who still had proteinuria at the end of 4 weeks of prednisone treatment were considered to be steroid resistant. In steroid-resistant patients and those with frequent relapses, intravenous pulse methylprednisolone or cyclophosphamide were used.[6] Fifty age- and sex-matched normal subjects from a local school or kindergarten served as controls. These subjects had normal blood pressure (BP), no clinical electrocardiographic (ECG) or echocardiographic evidence of cardiovascular disease, and no evidence of pulmonary disease. Informed consent was obtained from the patients and controls or their guardians. The study was approved by the Hospital Human Investigation Review Board.

2.2. Echocardiography

Echocardiography was performed using a Toshiba SSH-140 color Doppler ultrasound system (Toshiba Corporation, Tokyo, Japan) with transducers of 3.75 MHz or 5 MHz, as appropriate for children or adolescents. A complete echocardiographic examination was performed to exclude the possibility of congenital heart disease. Later measurements were performed using the machine's incorporated analysis package. RV pressure and volume signals were recorded to quantify general hemodynamic conditions. Heart rate, stroke volume, cardiac output, RV end-diastolic volume, RV end-systolic volume, RV ejection fraction, RV end-diastolic pressure, RV peak systolic pressure, and RV end-systolic pressure were determined from pressure-volume loops. Stroke work was obtained as the area of the pressure-volume loop, and the maximal rates of RV pressure upstroke and fall (dP/dt_{max} and dP/dt_{min}, respectively) were calculated.[7] Effective pulmonary arterial elastance, as a measure of RV afterload, was calculated as end-systolic pressure divided by stroke volume.

2.3. Laboratory study

Concentrations of plasma tumor necrosis factor-α (TNF-α) and insulin-like growth factor-1 (IGF-1) were measured using commercial enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems Inc., Minneapolis, MN, USA), according to the manufacturer's specifications. A high sensitivity kit (Quantikine HS; R&D Systems Inc) was used to measure TNF-α and IGF-1 immunoactivity.

2.4. Clinical and ECG study

Twelve-lead ECG, BP and chest radiographs were recorded. Blood samples were collected for coagulation assays, platelet counts, and analysis of prothrombin time and biochemical indicators of renal disease (proteinuria, serum albumin, complement C_3, cholesterol, creatinine level).

2.5. Statistical analysis

Data are presented as mean ± SD. Means between two groups were compared using paired or unpaired Student's *t* tests, as appropriate. Non-parametric data were compared using Pearson χ^2 tests or Fisher's exact tests. The 95% confidence intervals were calculated as appropriate. Linear correlation and regression analyses were used to test the correlations between increased RV filling pressure and the independent variables. The Mann-Whitney U test was used to compare data that were not normally

distributed. SPSS 11.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis. A p value of less than 0.05 was regarded as significant.

3. Results

3.1. Clinical features

All children in the study group were considered to have PNS. Thirty-eight patients were at PNS onset; 12 patients were in relapse after remission. The time from onset of the disease ranged from 1 day to 9 years, with a median of 4.5 weeks. At the time of admission, all patients had edema, heavy proteinuria (>1.0 g/m^2/day), hypoalbuminemia [serum albumin <2.5 g/dL (25 g/L)] and hypercholesterolemia. Serum creatinine ranged from 40–116 μmol/L. Total platelet count averaged 323×10^9/L ($\pm 97\times 10^9$/L), and the prothrombin time was 13.3±1.4 seconds. Chest radiography revealed that 31 patients had pulmonary congestion. A total of 41 patients responded during initial treatment; nine were steroid-resistant. In steroid-resistant patients, data from percutaneous kidney biopsies were only available in three patients: two indicated membranoproliferative glomerulonephritis and one had FSGS. Intravenous pulse methylprednisolone and cyclophosphamide were used in 14 and 7 patients, respectively. No patients received any medication for their systemic hypertension. ECG was abnormal in 27 patients: of these, 15 had frequent ventricular or atrial (n=3) premature beats, and 12 had ST- or T-wave changes. In comparison to normal controls, patients with PNS had a larger RV dimension by echocardiography, and higher systolic and diastolic blood pressures.

RV function was determined by recording pressure-volume loops. In the 50 patients with PNS, RV end-diastolic pressure was raised by an average of 20% in 39 patients, whereas RV ejection fraction was reduced by an average of 15% compared with controls ($p<0.05$ for both). Cardiac output and stroke volume were maintained, indicating compensation at the expense of increased RV end-diastolic and end-systolic volumes and increased RV filling pressure ($p<0.05$).

Plasma TNF-α was elevated in patients with PNS (326±117 kU/L *vs.* 75±23 kU/L, $p<0.05$); IGF-1 levels were similar in PNS patients and controls (Table 1).

3.2. Relationships between RV function and risk factors for PNS

We investigated the relationships between the various risk factors for PNS and RV function. Assuming that all patients with no tricuspid regurgitation or with immeasurable regurgitation had normal RV end-diastolic pressure, the clinical features of patients with increased RV end-diastolic pressure are compared with those with normal RV end-diastolic pressure in Table 2. Patients with increased RV end-diastolic pressure had a longer duration since

Table 1 Clinical and echocardiographic data of 50 children with primary nephrotic syndrome (PNS) and 30 controls*

	Patients with PNS (n=50)	Controls (n=30)	p
Age (yr)	7.2±3.3	7.9±3.5	0.73
Heart rate (beats/min)	96±18	92±13	0.25
SBP (mmHg)	111±15	90±12	<0.05
DBP (mmHg)	73±14	62±10	<0.05
Left atrial dimension (mm)	25.1±3.6	20.7±2.6	<0.01
LVEDD (mm)	34.9±5.5	35.9±6.4	0.89
RVEDD (mm)	12.7±2.6	11.9±2.5	0.038
Ppeak (mmHg)	42±15	33±6	<0.01
PES (mmHg)	35±14	29±7	0.32
PED (mmHg)	6.1±2.4	3.9±2.5	<0.01
dP/dt_{Max} (mmHg/s)	2473±778	2709±790	0.76
dP/dt_{Min} (mmHg/s)	1781±675	1668±428	0.69
LVEF (%)	72.8±5.8	78.3±8.0	0.19
RVEF (%)	59.6±4.3	72.0±2.9	<0.05
TNF-α (kU/L)	226±87	75±23	<0.05
IGF-1 (nmol/L)	24.5±7.1	21.9±6.0	0.32

*Data presented as mean±SD. SBP=systolic blood pressure; DBP=diastolic blood pressure; LVEDD=left ventricular end diastolic dimension; RVEDD=right ventricular end diastolic dimension; Ppeak=RV peak pressure; PES=right ventricular end-systolic pressure; PED=right ventricular end-diastolic pressure; dP/dt_{max}=maximal rate of pressure increase; dP/dt_{min}=maximal rate of pressure decline; LVEF=left ventricular ejection fraction; RVEF=right ventricular ejection fraction; TNF-α=tumor necrosis factor-α; IGF-1=insulin-like growth factor-1.

Table 2 Comparison of cardiac examination results between patients with increased and those with normal right ventricle end-diastolic pressure (RVEDP)*

	Patients with increased RVEDP (n=39)	Patients without increased RVEDP (n=11)	p
Heart rate (beats/min)	102±19	99±20	0.819
SBP (mmHg)	116±18	108±15	0.734
DBP (mmHg)	76±14	77±17	0.898
Abnormal ECG changes	22 (56.4%)	5 (45.5%)	0.434
Left atrial dimension (mm)	26.2±2.8	23.4±2.3	0.355
LVEDD (mm)	36.4±5.5	34.9±4.8	0.447
RVEDD (mm)	13.7±2.6	12.3±2.0	0.064
LVEF (%)	69.7±4.8	71.4±4.4	0.316
RVEF (%)	60.1±4.3	58.9±3.8	0.545
TNF-α (kU/L)	257±97	198±67	<0.01
IGF-1 (nmol/L)	24.9±3.1	24.4±6.4	0.510
Duration since onset (wk)	115±35	24±6	0.015
Steroid resistant (n)	7	2	0.478

*Data presented as mean±SD, n (%) or n. SBP=systolic blood pressure; DBP=diastolic blood pressure; ECG=electrocardiography; LVEDD=left ventricular end diastolic dimension; LVEF=left ventricular ejection fraction; RVEF=right ventricular ejection fraction; RVEDD=right ventricular end diastolic dimension; TNF-α=tumor necrosis factor-α; IGF-1=insulin-like growth factor-1.

Table 3 Clinical and echocardiographic data of 50 children with nephrotic syndrome in relation to steroid responsiveness*

	Non-steroid dependent (n=36)	Steroid dependent (n=5)	Steroid resistant (n=9)
Age (yr)	5.3±3.6	6.0±4.5	6.1±3.3
Heart rate (beats/min)	95±19	94±17	98±18
SBP (mmHg)	102±14	110±18	111±22
DBP (mmHg)	75±16	82±18	85±19
Left atrial dimension (mm)	23.4±2.5	25.7±3.0	26.1±3.4
LVEDD (mm)	33.6±4.6	35.8±6.6	37.1±6.0
RVEDD (mm)	10.9±2.5	11.0±3.0	11.2±3.1
TNF-α (kU/L)	45±19	44±17	47±17
IGF-1 (nmol/L)	5.1±2.1	5.0±1.7	4.8±2.0
LVEF (%)	68.6±6.2	72.3±8.0	71.8±7.9
RVEF (%)	59.1±3.5	62.3±4.9	61.7±5.5

*Data presented as mean±SD. SBP=systolic blood pressure; DBP=diastolic blood pressure; LVEDD=left ventricular end diastolic dimension; RVEDD=right ventricular end diastolic dimension; TNF-α=tumor necrosis factor-α; IGF-1=insulin-like growth factor-1; LVEF=left ventricular ejection fraction; RVEF=right ventricular ejection fraction.

disease onset (p=0.015) and a higher plasma TNF-α level (p<0.01). There were no differences in terms of age, steroid dependence, steroid resistance (Table 3), biochemical indicators of PNS and coagulation, or the presence of pulmonary congestion (p>0.05 for all). Further comparisons between the two groups with respect to cardiac signs and cardiac laboratory test results found no significant differences in left ventricular systolic or diastolic function, BP or any other parameters. RV systolic pressure only correlated weakly with RV dimension (r=0.44, p<0.05). There were no correlations between RV systolic pressure and any biochemical indicators of PNS or coagulation (p>0.05 for all).

4. Discussion

Patients with chronic renal failure (CRF) manifest increased cardiac morbidity and mortality compared with age-matched controls. This is mainly due to hypertension, electrolyte disorders, volume overload and anemia.[8] Indices of altered renal function such as microalbuminuria, overt proteinuria, increased serum creatinine concentration, or reduced estimated glomerular filtration rate are independent predictors of cardiac morbidity and mortality.[9,10] Most of the clinical observations of cardiac complications of CRF have been made in adults, especially those with diabetes mellitus and hypertension.

Cardiac disease in these patients mostly takes the form of myocardial infarction. The emerging importance of cardiac disease in children and young adults with end-stage renal disease is highlighted by a recent report indicating that cardiovascular deaths accounted for 23% of the mortality in this population.[11] However, the relationship between cardiac disease and CRF and the various types of PNS, in particular, has not been sufficiently studied in pediatric patients. In the present study, we evaluated RV function in children with PNS using Doppler echocardiography. Apart from RV hypertrophy, the primary cardiac response in PNS was RV dysfunction, that is, increased RV end-diastolic volume and pressure with consequent reductions in RV ejection fraction. This indicated that pulmonary arterial pressure was increased in patients with PNS.

The etiologies of RV dysfunction in children with PNS have been unclear until recently. However, the current study demonstrated that increased RV peak pressure and RV end-diastolic pressure were associated with a longer time since disease onset, though no other factors predictive of or related to increased RV peak pressure and RV end-diastolic pressure could be identified in children with PNS. However, we suggest that increased RV peak pressure and RV end-diastolic pressure in children with PNS could be ascribed to the following:

First, impaired functional reserve was highlighted by hemodynamic stress with increased RV end-diastolic pressure. Acute afterload elevations would result in decreased relaxation rate and increased diastolic intolerance to afterload in children with PNS. The hemodynamic disturbance was caused by increased diastolic intolerance to afterload. This response to acute afterload can be a precocious sign of dysfunction, preceding overt heart failure.[12]

Second, the elevated RV peak pressure and RV end-diastolic pressure could be caused by pulmonary arterial hypertension. Hypercoagulability can be caused by profound abnormalities in almost all coagulation factors and clotting inhibitors, as well as by defects in platelets and the fibrinolytic system. Although pulmonary embolism appears to be rarer in children than in adults,[2] its incidence might be underestimated because of the high number of asymptomatic or subclinical events in children with PNS.[13] Even in adults, as many as 50% of episodes of acute pulmonary thromboembolism remain undetected because their clinical presentation mimics the characteristics of a number of other disease entities, and the sensitivity and specificity of diagnostic tests for pulmonary embolization remain either weak or poorly defined.[14] It is therefore possible that some of our patients might have developed pulmonary embolism either during or before the present episode of PNS. Our results were unable to identify any relationship between increased pulmonary pressure and the biochemical indicators of thromboembolism studied. This could be because of wide variations in these indicators, or because of the small number of patients with increased pulmonary pressure.

Systemic hypertension is a third possible explanation for the increased RV peak pressure and RV end-diastolic pressure observed in children with PNS. BP was higher in children with PNS compared with controls. Sustained systemic hypertension has been shown to be a risk factor for increased pulmonary arterial pressure.[15] However, our results failed to detect any significant difference in blood pressure between patients with normal RV peak pressure and RV end-diastolic pressure, and those with increased RV peak pressure and RV end-diastolic pressure. Thus, the duration of systemic hypertension might be a more important contributory factor in the increased RV peak pressure and RV end-diastolic pressure than the BP itself, because patients with increased RV peak pressure and RV end-diastolic pressure had longer durations since PNS onset.

Cardiac edema could also account for myocardial dysfunction. Cardiac edema has been shown to increase myocardial stiffness and induce contractile dysfunction. This has been attributed to increased myocardial expression of aquaporins.[16] We cannot exclude the possibility that sympathetic activity may have influenced heart function in this study. Further studies are needed to determine the role of sympathetic activity. Additionally, regarding the role of proinflammatory cytokines, TNF-α levels were upregulated in the children with PNS. These observations mimic the pattern of cytokine activation observed in the glomeruli of rats injected with puromysin aminonucleoside, and might partly be explained by the increased circulating levels of TNF-α reported in PNS or the self-induction of TNF-α even in remote organs.[17–20] Local production of proinflammatory cytokines such as TNF- α in the heart is potentially relevant, given its well-known role in cardiac remodeling and contractile dysfunction.[21,22] Moreover, TNF- α is a major determinant of cachexia in several chronic diseases.[23,24] Disturbed cardiomyocyte calcium kinetics have also been implicated in myocardial dysfunction during heart failure progression.[12] No changes in circulating levels of IGF-1 were detected in the current study, suggesting that this pleiotropic growth factor is not involved in cardiac remodeling. Given that anorexia contributes to the malnutrition observed in PNS, the control of food intake might also be a relevant factor.[25]

In conclusion, the results of this study showed that increased RV peak pressure and RV end-diastolic pressure occurred in 78% of children with

PNS, together with elevated plasma TNF-α levels. Further studies are needed to understand the etiology, clinical implications, and long term prognosis of this abnormality.

References

1. Citak A, Emre S, Sairin A, et al. Hemostatic problems and thromboembolic complications in nephrotic children. *Pediatr Nephrol* 2000;14:138–42.
2. Lilova MI, Velkovski IG, Topalov IB. Thromboembolic complications in children with nephrotic syndrome in Bulgaria (1974–1996). *Pediatr Nephrol* 2000;15:74–8.
3. Olanrewaju A, Rachel F, Suzanne V, et al. Cardiac disease in children with primary glomerular disorders—role of focal segmental glomerulosclerosis. *Pediatr Nephrol* 2004;19: 408–12.
4. Gerald F, Susan H, Gursharan K, et al. Vascular function of the peripheral circulation in patients with nephrosis. *Kidney Int* 2001;60:182–9.
5. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at the time of diagnosis. *Kidney Int* 1978;13:159–65.
6. British Association for Paediatric Nephrology and Royal College of Physicians. Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. Report of a Workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. *Arch Dis Child* 1994;70:151–7.
7. Leeuwenburgh BP, Steendijk P, Helbing WA, et al. Indexes of diastolic RV function: load dependence and changes after chronic RV pressure overload in lambs. *Am J Physiol Heart Circ Physiol* 2002;282:H1350–8.
8. Hannedouche T, Bouiller M, Caillard S. Absolute cardiovascular risk among nephrology patients. *Nephrologie* 1998; 19:197–201. [In French]
9. Segura J, Campo C, Ruilope LM. Proteinuria: an underappreciated risk factor in cardiovascular disease. *Curr Cardiol Rep* 2002;4:458–62.
10. Ritz E, Dikow R, Ruilope LM. Renal dysfunction as a cardiovascular risk factor. *Curr Hypertens* 2002;Rep 4:365–8.
11. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end stage kidney disease. *J Pediatr* 2002;141:191–7.
12. Correia Pinto J, Henriques-Coelho T, Roncon-Albuquerque Jr R, et al. Differential right and left ventricular diastolic tolerance to acute afterload and NCX gene expression in Wistar rats. *Physiol Res* 2006;55:513–26.
13. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657–62.
14. Eterson KL. Acute pulmonary thromboembolism: has its evolution been redefined? *Circulation* 1999;99:1280–3.
15. Alpert MA, Bauer JH, Parker BM, et al. Pulmonary hemodynamics in systemic hypertension. Long-term effect of minoxidil. *Chest* 1979;76:379–83.
16. Egan JR, Butler TL, Au CG, et al. Myocardial water handling and the role of aquaporins. *Biochim Biophys Acta* 2006; 1758:1043–52.
17. Gomez-Chiarri M, Ortiz A, Lerma JL, et al. Involvement of tumor necrosis factor and platelet-activating factor in the pathogenesis of experimental nephrosis in rats. *Lab Invest* 1994;70:449–59.
18. Bustos C, Gonzalez E, Muley R, et al. Increase of tumour necrosis factor alpha synthesis and gene expression in peripheral blood mononuclear cells of children with idiopathic nephrotic syndrome. *Eur J Clin Invest* 1994;24: 799–805.
19. Suranyi MG, Guasch A, Hall BM, et al. Elevated levels of tumor necrosis factor-alpha in the nephrotic syndrome in humans. *Am J Kidney Dis* 1993;21:251–9.
20. Nakamura H, Umemoto S, Naik G, et al. Induction of left ventricular remodeling and dysfunction in the recipient heart after donor heart myocardial infarction: new insights into the pathologic role of tumor necrosis factor-alpha from a novel heterotopic transplant-coronary ligation rat model. *J Am Coll Cardiol* 2003;42:173–81.
21. Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. *Circulation* 1996;93:704–11.
22. Torre-Amione G, Kapadia S, Lee J, et al. Expression and functional significance of tumor necrosis factor receptors in human myocardium. *Circulation* 1995;92:1487–93.
23. Jackman RW, Kandarian SC. The molecular basis of skeletal muscle atrophy. *Am J Physiol Cell Physiol* 2004;287: C834–43.
24. Moldawer LL, Copeland III EM. Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. *Cancer* 1997;79:1828–39.
25. Dong F, Ren J. Insulin-like growth factors (IGFs) and IGF-binding proteins in nephrotic syndrome children on glucocorticoid. *Pharmacol Res* 2003;48:319–23.