Prednisone/Cyclophosphamide treatment in adult-onset autosomal dominant familial focal segmental glomerulosclerosis (FSGS 1)

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Abstract

Familial FSGS is a heterogeneous disease characterized by proteinuria and an unremitting deterioration of the excretory function. FSGS 1 is a less severe form of familial FSGS with autosomal-dominant inheritance, adult onset and slow progression to end-stage renal failure. Previous studies showed steroid unresponsiveness or variable response to steroids, cyclophosphamide and ACE inhibitors, and low rate of recurrence after transplantation.

We treated with steroids/cyclophosphamide 8 patients (3 families) with FSGS1 (aged 24±3,11) and compared the results to 20 patients with idiopathic FSGS (aged 35±2), and 6 untreated patients with familial form. The treatment included prednisone 0,5mg/kg/daily for 4 months with slow tapping over to 20mg daily for further 6 months and cyclophosphamide 50mg daily 6 months, alternate use after. The follow-up period was two years.

None of the patients with idiopathic FSGS experienced end-stage renal failure during follow-up (serum creatinine 115±10, to 183,4±65 μmol/l) and proteinuria decreased (5,42±0,84 to 4,68±1,2g/d). One FSGS 1 patient died because of intracranial hemorrhage, 2/8 started dialysis within two years, but 5/8 presented similar results as control group: slow increase of creatinine form 130,62±15,91 to 215,78±63,62 μmol/l and slight decrease of proteinuria from 4,69±0,81 to 3,28±0,24g/d. All untreated patients with FSGS1 experienced end-stage renal failure within two years.

Both forms of adult-onset FSGS, idiopathic and familial presented slow deterioration of the renal function under immunosuppression, but we can not say that they are good responders: complete or partial remission was not noted. The number of treated patients is small to make exact conclusions.

Key words: familial focal segmental glomerulosclerosis, prednisone, cyclophosphamide

Introduction

The discovery of molecular effects of podocyte components causing familial forms of nephrotic syndrome suggested the role of podocytes as the site of permselectivity in the kidney (1). Since then, knockout models of podocyte components and further molecular genetic screenings definitely consolidated this concept (1,2). Nephrin (NPHS1) was the first podocyte protein to be found mutated in association with a rare form of congenital nephrotic syndrome with autosomal recessive inheritance. Podocin (NPHS2) was the second recognized protein to cause proteinuria in familial cases with recessive inheritance and in sporadic patients (1,2,3). The clinical picture of nephrotic syndrome caused by podocin mutations ranges from an early onset, resembling congenital nephrotic syndrome to a late onset in the second decade of life, resembling idiopathic focal segmental glomerulosclerosis (1,5). Finally, α-actinin 4 was the most recognized structural component of the podocyte causing proteinuria in rare cases of dominant nephrotic syndrome in adults. So, the familial forms of FSGS are caused by mutations in genes at (1,6):

- 1q25-31 for NPHS2, autosomal recessive form, and
- 11q21-22, and 19q13 for α-actinin 4, autosomal dominant form of FSGS (FSGS1)

Patients with autosomal recessive form do not respond to standard steroid treatment of nephrotic syndrome and exhibit a decreased risk of FSGS recurrence after kidney transplantation (7-9).

The aim of our study was to analyze the responsiveness to prednisone/cyclophosphamide treatment in two groups of patients: (I) patients with adult-onset autosomal dominant familial FSGS (1) and (II) patients with idiopathic FSGS.

Patients and methods

Selection of the patients

3 groups of patients were included in the study.

1. 8 patients (3 families) with FSGS1 aged 24±3,11, treated.
2. 20 treated patients with idiopathic FSGS aged 35±2
3. 6 untreated patients with FSGS 1 (treated only with supportive treatment), aged 26±4,2.

Treatment and follow-up

Prednisone 0,5mg/kg/daily was performed for 4 months with slow tapping over to 20mg daily for the further 6 months, then continuing with this dosage to the end of the study. The daily dosage of cyclophosphamide for the first 6 months was 50mg, alternate day use was performed later. The whole follow-up period was two years. Laboratory investigations were performed monthly.

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Results

Idiopathic FSGS

None of the patients experienced end-stage renal failure during follow-up. Serum creatinine presented slight, non significant increase, from 115±10, to 183,4±65 μmol/l, p>0,05. Proteinuria decreased, but also non-significantly, from 5,42±0,84 to 4,68±1,2g/daily, p>0,05. So we did not noted partial or complete remission of the nephrotic syndrome.

FSGS1 patients – treated

One of the patients, 20-year old, female, died because of intracranial hemorrhage due to severe form of hypertension.
2/8 patients started dialysis within two years, one after 18 months, the other after 6 months. The second patient (male, 18 years) was transplanted after two months dialysis treatment without evidence of recurrence during the follow-up.
5/8 patients presented similar results as idiopathic form. Slight, but significant increase of serum creatinine was noted in this group of patients, from 130,62±15,91 to 215,78±63,62 μmol/l, p<0,05. Proteinuria decreased non-significantly (p>0,05), from 4,69±0,81 to 3,28±0,24g/daily, so it was still in nephrotic ranges.

FSGS1 patients – untreated

The results at the end of the study were catastrophic. At start, their mean value of serum creatinine was not significantly different comparing to previous two groups: 167,92±45,21 μmol/l. All six patients experienced end-stage renal failure within two years.

Discussion

There are many studies on genetic disorders in familial forms of FSGS (1-3,10-13), but the experience with the treatment of these cases is poor, so it is very difficult for us to compare our results. It was accepted that nephrotic syndrome in familial forms of FSGS is steroid resistant (2,7,11,13). Patients with homozygous or compound heterozygous mutations in NPHS2 exhibit primary steroid resistance and a decreased risk of FSGS recurrence after kidney transplantation (7). There was published a study in 2004 which tested this hypothesis comparing the results between two groups of patients: 1)190 patients with familial FSGS and 2) 124 patients with idiopathic FSGS (7). Recurrence of the disease was noted in only 8% of familial form, but in 35% of idiopathic form. Because of steroid unresponsiveness of familial form, the patients in this study were treated with cyclosporine A and cyclophosphamide with partial response. Besides small number of patients we noted some encouraging results: 5/8 treated patients did not develop end stage renal failure after two years and all untreated ones did.

Conclusions

The small number of patients did not allow us to perform standard statistic methods in order to make exact conclusions. It is also unclear what can be the mechanism of the drug acting in the patients who responded and did not worsen their renal function.

References

1. Caridi G *et al*. Broadening the spectrum of diseases related to podocin mutations. *J am Soc Nephrol* 2003; 14: 1278-1286
2. Pollak MR. The genetic basis of FSGS and steroid-resistant nephrosis. *Semin Nephrol* 2003; 23: 141-146
3. Winn MP. Approach to the evaluation of heritable diseases and update of familial focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2003; 6: vi14-20
4. D'agati V. Pathologic classification of focal segmental glomerulosclerosis. *Semin Nephrol* 2003; 23: 117-134
5. Winn MP *et al.* Clinical and genetic heterogeneity in familial focal segmental glomerulosclerosis. International collaborative group for therapy of familial focal segmental glomerulosclerosis. *Kidney Int* 1999; 55: 1241-1246
6. Rana K *et al*. Clinical, histopathologic, and genetic studies in nine families with focal segmental glomerulosclerosis. *Am J Kidney Dis* 2003; 41: 1170-1178
7. Ruf RG *et al.* Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. *J Am Soc Nephrol* 2004; 15: 722-732
8. Weber S *et al*. NPHS2 mutation analysis shows genetic heterogeneity of steroid resistant nephrotic syndrome and low post-transplant recurrence. *Kidney Int* 2004; 66: 571-579
9. Yorgin PD, Belson A, Higgins J, Alexander SR. Pulse methylprednisolone, cyclosporine, and ace inhibitor therapy decreases proteinuria in two siblings with familial focal segmental glomerulosclerosis. *Am J Kidney Dis* 2001; 37: E44
10. Conlon PJ *et al*. Spectrum of disease in familial focal and segmental glomerulosclerosis. *Kidney Int* 1999; 56: 1863-1871
11. Ekim M *et al*. Three siblings with steroid-resistant nephritic syndrome: new NPHS2 mutations in a Turkish family. *Am J Kidney Dis* 2004; 44: 10-12
12. Koziell A *et al*. Genotype/phenotype correlations of NPHS1 and NPHS2 mutations in nephrotic syndrome advocate a functional inter-relationship in glomerular filtration. *Human Molecular genetics* 2002; 11: 379-388
13. Karle SM *et al.* Novel mutations in NPHS2 detected in both familial and sporadic steroid-resistant nephritic syndrome. *J Am Soc Nephrol* 2002; 13: 388-393