MUTATIONS IN INFANTIL NEPHROTIC SYNDROME AND WORSE PROGNOSTIC RESULTS OF E117K POLYMORPHISM IN NPHS1

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Objectives:

Nephrotic syndrome (NS) is diagnosed by the presence of proteinuria, edema, hypoalbuminemia and hyperlipidemia. NS can be classified according to age of onset or treatment response, but there is no common concept about this. Clinically if onset used for classification of NS divided as congenital (CNS), infantile and childhood. CNS refers to disease that is present at birth or with in the first three months of life (1-3). Later onset, between three months and one year of age, is called infantile nephrotic syndrome (INS). Up to now, genetic basis was reported to be responsible from two thirds of early onset NS cases (1, 2,3). Mutations in NPHS1 and NPHS2 were reported to be responsible for 60% of early onset NS (1, 2).

In this study we evaluated children with infantile NS, showed the mutational analysis of NPHS1 and NPHS2 besides phenotypic features. The focus of this study was to evaluate genotypic and phenotypic features of both NPHS1 and NPHS2.

Methods:

- We have evaluated clinical data, mutation analysis, histology, treatment modalities and outcome of 48 children with familial or sporadic infantile NS Children carrying syndromic findings and having recurrence after kidney transplant were excluded from study.
- Forty- eight patients belonging to 44 families were classified as having infantile NS with first documented presentation between 3rd months and the end of 12th.
- The clinical diagnosis of NS required the presence of heavy proteinuria (> 40 mg/m²/h or urine protein/creatinine ratio > 2 mg/mg), edema, hypoalbuminemia (< 2.5 mg/dL) and also hyperlipidemia. Complete response was defined as both clinical healing and disappearance of proteinuria in the urine of three consecutive days. A partial response was defined as the disappearance of edema, an increase in the serum albumin concentration and the persistence of proteinuria below nephrotic range. Steroid resistance was defined as failure to enter into remission after 4 weeks of prednisone treatment (4).
- All renal biopsy specimen were analyzed by the same pathologist, were processed for light microscopy and immunofluorescence staining. Patients were enrolled to study after an informed consent taken for their parents and faculty ethical comitte approved the study.
- Patients were classified into 3 groups; group 1: included cases having only NPHS1 mutation, group 2: included cases with only NPHS2 mutation, group 3: cases without any mutation. Mutation analysis of NPHS1 and NPHS2 performed in all cases, with the mutation rate of 58.3% (28 out of 48).

Results:

- The mean age at the onset of nephrotic syndrome was 8.7 ± 2.3 months and the mean follow up was 8.3 years. Parental consanguinity was found in 12.5% of the families. Seven familial and 41 sporadic cases were found.
- Kidney biopsy was performed in 45 out of 48 patients, showed focal segmental glomerulosclerosis in 29 (29/45; 65%), IgM nephropathy (IgMN) in 6 (6/45; 13%) and minimal change disease (MCD) in 10 patients (10/45; 22%).
- Group 1 included patients having only mutations of NPHS1 in 5 cases (10, 4%) and group 2 included patients having only mutations of NPHS2 in 13 (27%). Thirty cases (62.5%) had neither NPHS1 nor NPHS2 mutation placed in group 3 (Table 1).
- Initially, all patients had normal renal function except one . Patients were given to steroid, cyclosporine, cyclophosphamide, and rituximab. At the end of follow up time (8.3 years), there were 32 children with partial (n=20) or complete response (n=12) and 16 without any response. Among the non-responsive 16 cases, 6 developed CKD stages 2-4 and 10 progressed to CKD stage 5 (ESRD) (Table 1).
- Mutational distribution of the ESRD cases were as followed: 1 case with NPHS1 (V709G), 4 cases with NPHS2 mutation (P20L, R168H, 467/7 insertion T), last 5 were without any NPHS1 and 2 mutations. The median duration for progression to ESRD from onset of disease was 36.1 ± 51.9 months.
- All 10 ESRD cases were transplanted at a median age of 68.9 ± 43.6 months, with only one rejection due to recurrence of disease. The ESRD ratio (4/10; 40%) was found highest in the patients with NPHS2 mutation, followed by non-mutated group (5/20; 25%) and 1 in NPHS1 mutated cases (1/15; 6.7%) (Table 2).

Table 1. Demographic, clinical and genetic features of groups.

Variables	Patients with NPHS1 mutation (group 1)	Patients with NPHS2 mutation (group 2)		Patients without any mutation (group 3)		
		Without E117K	With both E117K	Patients with E117K polymorphism EK	Patients with E117K polymorphism KK	Patients without any mutation
Patient number	5	10	3	6	4	20
Gender (male/female)	3/2	5/5	2/1	4/2	2/2	13/7
Age of disease onset (month)	7.9+-3.9	8.32+-3.01	8.6+-2.5	6.2+-1.8	6.3+-0.8	9.9+-2.4
Number of attacks	4/patient	6.2/patient	4.3/patient	6.1/patient	3.8/patient	7.1/patient
Response to treatment (complete/partial/no)	3/-/2	-/3/7	-/2/1	2/3/1	-/3/1	7/9/4
Proteinuria mg/m2/h /Cr. Cle. ml/dk/m2	51.7+14.3 /67.1+-29.0	67.2+-21 /32.3+-16	37.1+-9.7 /35.8+-11.2	12.3+-6.1 /86+-9.2	43.2+11.9 /87.1+12.1	128.3+-22.9 /22.3+-27.1
CRD	-	1	1	1	1	2
ESRD	1	4	-	-	-	5

Table 2. Comparison of patients with E117K mutation with patients without nephrin mutation but having podocine mutation, with other nephrin mutations, with patients without any nephrin mutation

	Patients with E117K mutation (n:10)	Patients without nephrin mutation but having podocine mutation (n:10)	P	Patients without nephrin and podocine mutation (n:20)	P	Patients without any mutation (n:30)	P	Patients with other nephrin mutations (n:5)	P
Disease onset (months)	6,21±1.9	8.32± 3.01	SD²: 6.3 t:1.87 p<0.05	9.99±2.4	SD²: 5.07 t:4.36 p<0.0005	9.43±2.7	SD²: 6.41 t:3.47 p<0.05	7,93±3,9	SD²: 5.72 t:0.91 p>0.1
Familial /Sporadic	0/10	3/7	x²: 3.52 p>0.05	3/7	x²: 1.67 p>0.1	6/24	x²: 3.34 p>0.1	1/4	x²: 3.65 p>0.05
Histology (FSGS / Others)	4/6	7/3	x²: 1.82 p>0.1	12/20	x²: 1.87 p>0.1	19/11	x²: 1.68 p>0.1	3/-	x²: 3.36 p>0.05
ESRD	0	4	x²: 5 p< 0.05	5	x²: 2.98 p>0.05	8	x²: 3.34 p>0.05	1	x²: 3.64 p>0.05
CRD	2	1	x²: 0.39 p>0.2	2	x²: 0.56 p>0.2	3	x²: 0.68 p>0.2	0	x²: 0.75 p>0.2

Conclusions:

In the current screening, we showed the genotypic and phenotypic features of infantile NS. We found that Infantile NS with podocin mutation have bad prognosis according to exonal distribution. NPHS1 mutations were found as a cause of severe and early disease type but better prognosis. Besides, E117K mutations of NPHS1 showed the similar course with other NPHS1 and NPHS2 mutations, only difference of that manifested relatively earlier onset. Also among NPHS1 mutations, E117K had been reported as polymorphism, but we showed our contrary findings and asked if does it a still polymorphism?

References:

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