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ORIGINAL ARTICLE

Do glutathione-S-transferase polymorphisms influence response to intravenous cyclophosphamide therapy in idiopathic nephrotic syndrome?

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Abstract The response to cyclophosphamide (CP) is variable and difficult to predict in children with idiopathic nephrotic syndrome (INS). The polymorphic expression of glutathione-S-transferase (GST) may affect the remission rate after CP therapy. In this study, we evaluated the correlation of GST polymorphism and response to CP in INS. We studied GST polymorphism in 74 children with steroid-sensitive (44) and steroid-resistant (30) INS receiving intravenous cyclophosphamide (IVCP) therapy. We correlated GSTM1, GSTT1, and GSTP1 genotypes with response to IVCP. Thirty-seven (50%) out of 74 children responded to CP therapy. A synergistic effect of three genotypic combinations showed significant correlation with remission in the steroid-sensitive group. These combinations were GSTP1 and GSTM1 null genotype (p=0.013) and GSTP1 together with GSTM1 and GSTT1 null genotypes (p=0.026). Further, a significant difference was observed with a combination of GSTM1 and GSTT1 null genotypes and Val105 polymorphism. No association was observed among steroid-resistant patients. Our results indicate that among children with steroid-sensitive NS, there is an association with response to IVCP therapy and combination of GSTP1 Val105 polymorphism and the null genotypes of GSTT1 and GSTM1. GST polymorphism may be of significance in the management of children with INS receiving CP therapy.

Keywords Nephrotic syndrome (NS) · Immunosuppressant therapy · Glutathione-S-transferase · Polymorphism · Cyclophosphamide

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Introduction

Idiopathic nephrotic syndrome (INS) is one of the commonest kidney disorders in children. Although the majority of these children respond to steroids, 40–50% show frequent relapses (FR) or steroid dependence (SD) [1]. Increasing dose of steroids leads to toxicity, requiring the use of potentially toxic drugs such as cyclophosphamide, chlorambucil, and cyclosporin A to achieve long-term remission. Many studies have shown that the best long-term remission rates are achieved with cyclophosphamide (CP) [2–6]. The average response rate to CP in various studies ranges from 28% to 75% in SD and from 24% to 70% in FR at 1–3 years [3]. Intravenous CP (IVCP) therapy has been used in children with steroid resistance, but the response varies [7]. A recent meta analysis has shown that only one third of patients treated with CP achieve a sustained remission [8]. Thus, the success of CP is difficult to predict. Evidence demonstrates that the total dose per body surface area (BSA) may influence the response in breast cancer patients [9]. In children with NS, steroid responsiveness predicts response to CP; children who are

FR or are SD respond much better to CP compared with steroid-resistant (SR) children. Glutathione-S-transferase (GST) polymorphisms may affect the metabolism of CP and the blood levels attained [10–12]. This in turn may also influence the response to CP in children with INS. However, there is a paucity of information regarding the correlation of these polymorphisms and response to CP in these children.

Hence, this study was conducted to evaluate the association of GST polymorphisms (GSTT1, GSTM1, and GSTP1) and correlate it with response to CP therapy in children with NS. To the best of our knowledge, this is the largest study evaluating the relationship of GST polymorphisms and response to CP among children with NS.

Patients and methods

We prospectively studied 74 consecutive children with INS requiring CP therapy. They were under regular follow-up in the nephrotic clinic of our institute. Informed written consent was obtained from their parents. All cases fulfilled the International Study of Kidney Disease in Children criteria for the diagnosis of NS. These children were subjected to standard prednisone therapy as per Ar beitsgemeinschaft für pädiatrische Nephrologie (APN) protocol. Based on the response to steroids, patients were classified into one of the steroid response categories as per criteria defined in an earlier study [3]. On the basis of steroid response pattern, these children were categorized into infrequent relapser (IFR), FR, SD, or nonresponders (NR). CP was given intravenously in monthly pulses of 500 mg/m^2 for 6 months in FR, SD, and NR subgroups.

Inclusion criteria were (1) steroid-sensitive NS (SSNS) with FR (FR = two or more relapses in a 6-month period following cessation of steroid therapy) or SD (SD = at least two consecutive relapses during steroid tapering or within 2 weeks of stopping steroid therapy), (2) steroid-resistant NS (SRNS) with no response to steroid therapy for 4 weeks. Renal biopsies were done in all SRNS cases. Children with a history of cytotoxic drug use prior to CP were excluded from the study. Children with poor compliance and not on regular follow-up were also excluded. Venous blood samples were collected in ethylenediaminetetraacetate (EDTA) vials for extraction of genomic deoxyribonucleic acid (DNA). After six pulses of IVCP, children were followed up for 6 more months to look for relapse. On the last follow-up, SD patients were categorized as responders if they showed a remission for 6 months or more and as NRs if they relapsed before that period. SRNS patients were considered responders if they achieved remission. The study was approved by the ethical committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) and Department of Biotechnology, Government of India.

Blood samples for measuring serum biochemical and lipid profiles were obtained the morning after an 8-h fast. Three milliliters of venous blood was collected in EDTA vials, and the extraction of genomic DNA was done using a commercial kit (Qiagen). The polymorphisms evaluated in the study were GSTM1, GSTT1, and GSTP1. We used different forward and reverse primers and appropriate polymerase chain reaction (PCR) conditions for the analysis. Exon 7 of the *CYP1A*1 gene was coamplified and used as an internal control. All products were separated on 2% agarose gel and subsequently stained with ethidium bromide to visualize the bands. DNA from samples positive for GSTM1 and GSTT1 genotypes yielded bands of 215 bp and 480 bp, respectively, and the internal positive controls (CYP1A1) PCR product corresponded to 312 bp. The GSTP1 genotype showed a band of 176 bp of amplified product, which was digested with *Alw*261 and electrophoresed on 3% agarose gel. The presence of restriction site resulted into two fragments of 91 bp and 85 bp, indicating the G allele. If there were A/G polymorphisms, then there were three fragments: 176 bp, 91 bp, and 85 bp.

Statistical analysis

We correlated the interrelationships between GSTM1, GSTT1, and GSTP1 genotypes and their association with gender, age at diagnosis, steroid response category (SS/SR) and number of CP doses. The association between GST genotypes and occurrence of relapse was examined with conditional logistic regression analysis to calculate odds ratios (OR) and their 95% confidence intervals (CI). GST genotypes and genotype combinations were used as categorical variables in the analyses. A p value <0.05 was taken as statistically significant. Yates' correction was applied. All statistical analysis was done by using SPSS version 13.0.

Results

The study group consisted of 74 cases (54 boys, 20 girls), with mean age at NS onset being 5.2±4.4 years (range 0.6–18 years). Of the 74 children, 44 (60%) were SS and 30 (40%) were SR. Of the 30 SR children biopsied, 20 had focal segmental glomerulosclerosis (FSGS), six had diffuse mesangial proliferation, and four had minimal-change disease. Follow-up after CP treatment was 4.5±3.1 years.

Thirty-seven (50%) of the 74 children responded to CP therapy. The mean number of days of remission following CP therapy was 1,170 (range 180–2,160 days). SS children had a much greater response to CP (27/44, 61%) compared with SR patients (10/30, 33.3%). There was no difference between responders and NRs with respect to gender, age, or total CP dosage/kg of body weight. On evaluating the

frequency of GSTM1, GSTT1, and GSTP1 genotypes in the study group, we observed that the null genotype of GSTT1 was the commonest (47, 63.5%), followed by the GSTM1 null genotype (29, 39.2%), whereas the GSTP1 polymorphism was seen in 16 children (22%). There was no significant association of individual GST genotypes with response to CP.

The frequency distribution of GSTM1, GSTT1, and GSTP1 genotypes among responders and NRs of both the SS and SR groups is shown in Table 1. In the SS group (44), 27 (61%) children responded to CP therapy. The frequency of GSTM1 null genotype was 44.4% and GSTT1 null genotype 66.7%. However, there was no significant difference between frequencies of GSTM1 and GSTT1 among responders and NRs. Among the responders, GSTP1 homozygous wild-type (I/I) genotype was present in 81.5%, and the homozygous polymorphic (V/V) genotype was seen in 11.4%; 7.4% were heterozygous for the polymorphism (I/V). As enzyme levels are reduced both in heterozygotes and homozygotes; I/V and V/V genotypes were combined for the analysis. We observed no significant difference among responders and NRs (p=0.288) for this genotype. Even at an allelic level, there was no difference in the frequency of the V allele in responders compared with NRs (p=0.396).

A further analysis evaluated the correlation among various combinations of the genotypes in responders and NRs (Table 2). We observed a significant correlation among three genotypic combinations: (1) GSTP1 wild type (I/I genotype) with GSTM1 null genotype (p=0.0137), (2) GSTM1 null and GSTT1 null genotypes (p=0.038), and (3) GSTP1 wild type along with GSTM1 and GSTT1 null genotypes (p=0.026).

Among the SR group, there was a higher frequency of GSTM1 null genotype (30%) in NRs compared with responders (17%). However, the difference was not statistically significant. Similarly, no significant changes in the frequency of other genotypes were found (Table 1).

Table 1 Distribution of glutathione-S-transferase (GST) genotypes in responders and nonresponders to cyclophosphamide (CP) therapy in steroid-sensitive and steroid-resistant cases

Response to CP	Total 44 [*n* (%)]	Responders 27 [*n* (%)]	Nonresponders 17 [*n* (%)]	OR (95% CI)	*P* value
Steroid-sensitive cases					
GSTM1					
Present	29 (66.0)	15 (55.6)	14 (82.4)	0.268	0.104
Null	15 (34.0)	12 (44.4)	03 (17.6)	(0.622–1.154)	
GSTT1					
Present	14 (32.0)	09 (33.3)	05 (29.4)	1.2	1
Null	30 (68.0)	18 (66.7)	12 (70.6)	(0.322–4.47)	
GSTP1					
I/I	33 (75.0)	22 (81.5)	11 (64.7)	2.4*	0.2887
I/V	06 (13.6)	05 (18.5)	06 (35.3)	(0.598–9.64)	
V/V	05 (11.4)	0	0		
Allele I	72 (81.8)	78 (79.6)	46 (95.8)	1.769	0.3961
Allele V	16 (18.2)	20 (20.4)	02 (4.2)	(0.594–5.272)	
Steroid-resistant cases					
GSTM1					
Present	16 (53.0)	05 (50.0)	11 (55.0)	0.8182	1
Null	14 (47.0)	05 (50.0)	09 (45.0)	(0.179–3.745)	
GSTT1					
Present	13 (43.0)	03 (30.0)	10 (50.0)	2.333	0.4404
Null	17 (57.0)	07 (70.0)	10 (50.0)	(0.465–11.698	
GSTP1					
I/I	25 (83.4)	09 (90.0)	16 (80.0)	2.25*	0.64
I/V	04 (13.3)	01 (10.0)	04 (20.0)	(0.217–23.337)	
V/V	01 (3.3)	0	0		
Allele I	54 (90.0)	19 (95.0)	36 (90.0)	2.111	0.6563
Allele V	6 (10.0)	1 (5.0)	4 (10.0)	(0.22–20.256)	

OR odds ratio, *CI* confidence interval

* I/V and V/V combined and compared with I/I genotype

Table 2 Distribution of various combinations of genotypes among responders and nonresponders of steroid-sensitive and steroid-resistant case

Genotype	Steroid Sensitive (44)				Steriod Resistant (30)			
	Responders 27 [*n* (%)]	Nonresponders 17 [*n*(%)]	*P* value	OR (95% CI)	Responders 10 [*n* (%)]	Nonresponders 20 [*n* (%)]	*P* value	OR (95% CI)
Double: GSTP + GSTM								
P1M1	11 (40.7)	09 (52.9)	0.7997	1.296 (0.4762–3.528)	5 (50.0)	09 (45.0)	0.3604	0.657 (0.310–1.393)
P0M0	01 (3.7)	01 (5.9)	1.505	1.0 (0.0605–16.52)	01 (10.0)	02 (10.0)	1	0.483 (0.041–5.631)
P0M1	04 (14.8)	05 (29.4)	1	0.78 (0.1948–3.123)	0	02 (10.0)	0.4915	0.187 (0.009–4.065)
P1M0	11 (40.7)	02 (11.8)	0.0137	7.0 (1.45–33.798)	04 (40.0)	07 (35.0)	0.5062	0.505 (0.130–1.952)
GSTP + GSTM								
P1T1	07 (25.9)	03 (17.6)	0.3141	2.586 (0.6225–10.74)	03 (30.0)	09 (45.0)	0.1042	0.259 (0.062–1.079)
P0T0	03 (11.1)	04 (23.5)	1	0.7317 (0.1538–3.48)	01 (10.0)	03 (15.0)	0.612	0.310 (0.030–3.17)
P0T1	02 (7.4)	02 (11.8)	1.3838	1 (0.1344–7.438)	0	01 (5.0)	1	0.322 (0.126–8.242)
P1T0	15 (55.6)	08 (47.1)	0.1446	2.328 (0.8667–0.6251)	06 (60.0)	07 (35.0)	1	0.824 (0.239–2.815)
GSTM + GSTT								
M1T1	08 (29.6)	05 (29.4)	0.5494	1.282 (0.7853–2.093)	01 (10.0)	06 (30.0)	0.1028	0.102 (0.015–1.227)
M0T0	11 (40.7)	03 (17.7)	0.0385	1.762 (1.213–2.559)	03 (30.0)	5 (25.0)	0.7065	0.555 (0.120–2.57)
M0T1	01 (3.7)	0	1	2.023 (1.636–2.503)	02 (20.0)	04 (20.0)	0.6707	0.464 (0.078–2.753)
M1T0	07 (25.9)	09 (52.9)	0.783	0.8514 (0.4675–1.55)	04 (40.0)	5 (25.0)	1	1.3 (0.312–5.406)
Triple: GSTP + GSTM + GSTT								
P1M1T1	06 (22.2)	03 (17.6)	0.4839	1.386 (0.8275–2.321)	01 (10.0)	06 (30.0)	0.1028	7.25 (0.815–64.492)
P0M0T0	01 (3.7)	1 (5.9)	1.505	1.0 (0.0605–16.52)	01 (10.0)	01 (5.0)	1.5085	1 (0.596–16.775)
P1M0T0	10 (37.0)	2 (11.8)	0.0264	1.863 (1.305–2.685)	02 (20.0)	04 (20.0)	0.6707	2.154 (0.0363–12.769)
P0M0T1	0	0	–	–	0	01 (5.0)	1	3.102 (0.121–79.291)
P0M1T0	02 (7.4)	3 (17.6)	1	0.7905 (0.2645–2.362)	0	02 (10.0)	0.4915	0.186 (0.009–4.065)
P0M1T1	02 (7.4)	2 (11.8)	1.3838	1 (0.1344–7.438)	0	0	–	–
P1M0T1	01 (3.7)	0	1	2.023 (1.636–2.503)	02 (20.0)	03 (15.0)	1	1.556 (0.240–10.054)
P1M1T0	05 (18.6)	6 (35.3)	1	0.8974 (0.4528–1.779)	04 (40.0)	03 (15.0)	1	1.385 (0.282–6.798)

0 mutant genotype (GSTT and GSTM null genotype and GSTP I/V and V/V genotype), *1* wild-type genotype (GSTT and GSTM positive genotype and GSTP I/I genotype)
P value<0.05 was considered significant

In this group, the combination of genotypes also showed no correlation among responders and NRs (Table 2).

Discussion

It has been shown that GST polymorphisms influence survival in breast cancer, ovarian cancer, and risk of relapse after childhood leukemia [13]. It is known that GSTs catalyze glutathione conjugation of reactive CP metabolites and thereby influence blood levels of CP [14]. Hence, polymorphisms that result in reduced activity of these enzymes are likely to result in greater levels of active metabolites of CP and increased efficacy of CP.

GST is an important enzymatic system of the cellular mechanism of detoxification that protects cells against reactive oxygen metabolites due to the conjugation of glutathione with electrophilic compounds. GST enzymes are involved in the metabolism of xenobiotics that include environmental carcinogens, reactive oxygen species, and chemotherapeutic agents [11, 12]. In the GST, the μ subfamily is the most important polymorphism, encoding a partial gene deletion in GSTM1 and results in the complete absence of GSTM enzymatic activity [15]. At the GSTT locus, one polymorphism has been described, due to a gene deletion, known as the GSTT1 null allele. This polymorphism accounts for the variation in GSTT1 catalyzed metabolism of halo methanes by human erythrocytes. The GSTP1 wild-type allele contains adenine, whereas the GSTP1 polymorphic allele contains guanine at nucleotide position 313, producing Val105 instead of Ile105 in the protein. The GSTP1 Val105 polymorphism can result in reduced enzymatic activity compared with the wild-type form (Ile105). GSTM1 and GSTT1 exhibit a deletion

polymorphism, which in the homozygous state (GSTM1 null and GSTT1 null) leads to the absence of enzyme activity. GSTP1 Val105 polymorphism leads to reduced enzyme activity in heterozygous and homozygous conditions. Thus, these enzymes depict several polymorphisms with reduced enzyme activity.

In this study, the null genotype of GSTT1 was the commonest (68%) among all children with NS receiving CP. The GSTT1 null genotype is seen in 20–60% of individuals who do not express the enzyme. About 60% of Asians, 40% of Africans, and 20% of Caucasians do not express this enzyme [16]. The GSTP1 polymorphism has a population frequency of 30–40% in Caucasians, with heterozygotes (Ile/Val) being 40% and homozygotes (Val/Val) being 6% [17]. In our study, the frequency of the polymorphic genotype of GSTP1 was 22% (Ile/Val=13.5% and Val/Val=8.1%). We observed a significant association of GSTP1 Ile105 polymorphism with a combination of GSTM1 null and GSTT1 null genotype and response to CP therapy in our study population. Studies by Vester et al. have shown a significant effect of polymorphic expression of GST on the long-term remission rate after CP treatment in SSNS [18]. This study evaluated only 26 children with SSNS. It was observed that GSTM1 null genotype was shown to increase the efficacy of CP and that GSTP1 polymorphism was related to enhanced susceptibility to further relapses [18]. It was suggested that polymorphic expression of GSTM1 and P1 significantly influences the long-term remission rate, whereas GSTT1 genotype did not influence the outcome after CP treatment. In our study, the individual genotypes showed no relation to the response to CP, but the influence of the GSTP1 wild-type Ile105 polymorphism was seen in combination with other genotypes. An association was seen among children with a combination of GSTP1 wild-type genotype and GSTM1 null genotype (p=0.0137) and also with a combination of GSTM1 and GSTT1 null genotype (p=0.038). The presence of these three genotypes (GSTP1 wild type along with GSTM1 and GSTT1 null genotypes) also correlated with a response to CP therapy in these children (p=0.026).

Repeated use of corticosteroids in children with INS leads to steroid toxicity, which often requires the use of potentially toxic drugs such as CP, chlorambucil, and cyclosporin A to achieve long-term remission [19]. Of these, the best results to date are with CP. In contrast to the role of GSTs in environmental carcinogenesis, GST genotypes lead to lower enzyme activity, which may be of advantage for individuals undergoing chemotherapeutic treatment for neoplastic disease, as decreased detoxification enhances the effectiveness of cytotoxic drugs by prolonging their action in the body. Indirect evidence for the role of GSTs in modulating drug effects through deactivation of drug-generated hydroperoxides or other reactive oxygen species exists for adriamycin, mitomycin C, carboplatin, and cisplatin [20, 21].

Our results indicate that in children with SSNS, an association exists between a combination of GSTP1 Ile105 polymorphism and the null genotypes of GSTT and GSTM and response to CP therapy. However, in the SR group, the null genotypes of GSTM1 and GSTT1 and the GSTP Ile105 polymorphism were not associated with clinical response to CP. This could be due to the heterogeneity of SR cases. Hence a definite statement on the role of GST polymorphisms cannot be made in these patients. More studies involving larger population groups are needed to confirm this association. If proven, this might be a useful marker in helping to select children with NS who are likely to benefit from CP therapy.

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