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Association between N363S and BcLI Polymorphisms of the Glucocorticoid Receptor Gene (NR3C1) and Glucocorticoid Treatment-Related Side Effects in Acute Lymphoblastic Leukemia Patients: A Study from Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Objectives: To evaluate the association between N363S and BcLI polymorphisms of the NR3C1 gene and glucocorticoid treatment-related side effects in acute lymphoblastic leukemia patients. **Study design and setting:** A Cross-sectional study was conducted at the Department of Hematology, Hayatabad Medical Complex, Peshawar from January 2023 to December 2023. **Methods:** A total of 88 patients aging between 6 months to 25 years newly diagnosed with acute lymphoblastic leukemia were included in this study. Patients received induction chemotherapy, which included a glucocorticoid treatment regimen consisting of dexamethasone, administered at a dose of 6 mg/m² daily, which was continued for a duration of 28 days within the induction phase consisting of 6 weeks. Metabolic and biochemical parameters were measured at baseline and after completing the 28-day dexamethasone treatment course. Primary outcomes included evaluating the clinical manifestations of glucocorticoid treatment related side effects and association between polymorphisms of the Glucocorticoid Receptor Gene (NR3C1) and these adverse effects. **Results:** The mean age of patients in this study was 12.56 ± 5.1 years with an age range of 6 months to 25 years. The sample consisted of 70.5% males and 29.5% females. Glucocorticoid treatment significantly increased hyperglycemia ($p<0.001$), hypertension ($p=0.002$), hypertriglyceridemia ($p<0.001$), dyslipidemia ($p<0.001$), elevated ALT ($p=0.034$), elevated ALP ($p<0.001$), and Cushingoid features ($p<0.001$). In N363S genotype analysis, hyperglycemia ($p=0.03$) and hypertension ($p=0.02$) showed significant associations, while BcLI genotype showed no significant associations with any parameter. **Conclusion:** Genetic screening for NR3C1 polymorphism can enable personalized glucocorticoid therapy in the patients of Acute Lymphoblastic Leukemia to minimize treatment-related metabolic complications.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is characterized by the rapid proliferation of immature white blood cells, or lymphoblasts, in the bone marrow. This malignant hematologic disease is the most common type of leukemia in children and 80% of the disease is reported in children, however, it also affects and can prove devastating in adult patients.[1,2]

In patients suffering from ALL, Glucocorticoids (GCs) have been a cornerstone in the treatment by playing a vital role in achieving remission and enhancing survival. The potent anti-inflammatory and immunosuppressive properties of GCs play a crucial role in this treatment regimen by inducing apoptosis in leukemia cells and reducing the tumor burden. Due to these advantages, patients diagnosed with ALL are recommended intensive treatment comprising GCs in combination with a multi-drug chemotherapy regimen, while radiotherapy is also indicated in specific cases.[3,4] Commonly used GCs in ALL treatment are prednisolone and dexamethasone. GCs bind to the glucocorticoid receptor (GR), encoded by the *NR3C1* gene, which are located on the long arm of chromosome 5 (specifically 5q31), and influence various processes of cell function involved in the disease progression.[5]

With these significant efficacy benefits, CSs are found to be associated with a broad spectrum of adverse

side effects, affecting the quality of life and long-term health outcomes of ALL patients. The adverse events commonly reported in pediatric and adult oncology include metabolic disturbances (e.g., hyperglycemia, obesity), osteoporosis, hypertension, and psychiatric disorders. It is also stated in some research publications that the degree to which patients experience therapeutic efficacy and the risk of adverse effects varies significantly among patients. It is suggested that the variability in side effects may be due to the genetic factors influencing individual's response to GCs. The GR gene (NR3C1) is found to be responsible for initiating the cellular response to GCs and plays a pivotal role in mediating the effects of GC hormones.[6,7] Among the polymorphisms of the NR3C1 gene, two variants, N363S and BcLI, have taken specific attention in the context of GC sensitivity. These polymorphisms may modify the way in which GCs interact with their receptors, and can explain the varied clinical outcomes in ALL patients receiving GC therapy. The increased CS sensitivity of N363S polymorphism has been associated with enhanced therapeutic effects as well as increased side effects. On the other hand, the BcLI polymorphism has been associated with altered GR expression, thereby may affect its ability to mediate glucocorticoid actions.[8,9]

The genetic landscape of South Asian populations is distinct and exhibits unique characteristics that may influence the clinical significance of genetic polymorphisms. The issue becomes particularly concerning because ALL is one of the most prevalent pediatric hematological malignancies in Pakistan.[10]

This study was therefore aimed to evaluate the clinical manifestations of glucocorticoid treatment related side effects and association between polymorphisms of the GR gene (NR3C1) and these adverse effects in ALL Patients reporting at department of hematology Hayatabad Medical Complex Peshawar. The findings of this study will help to identify genetic markers that can guide personalized treatment strategies in ALL and improve patient outcomes.

METHODS

This cross-sectional study was conducted at the department of Hematology, Hayatabad Medical Complex Peshawar from January 2023 to December 2023, over a period of 1 year, after getting prior approval from ethical review board of the hospital.

Sample size was calculated with the following assumptions:

Prevalence of hyperglycemia during treatment= 16.5%, Precision=8%, population size=infinite. The estimated sample size (n) =83.[11]

A total of 88 patients aging between 6 months to 25 years and newly diagnosed with ALL were included in this study through consecutive sampling.

Exclusion criteria was set as patients who had previously been treated for ALL, patients who were already undergoing steroid therapy, those with other malignancies, and patients with known liver or kidney disease.

Consent form was taken from patient/ parents/ guardian prior to their enrolment in the study.

All the demographic characteristics and related clinical information were collected and pre-treatment metabolic and biochemical parameters were investigated.

Patients received induction chemotherapy as per the UK ALL 2011 protocol. This included a GC treatment regimen consisting of dexamethasone, administered at a dose of 6 mg/m² daily which was continued for a duration of 28 days within the induction phase consisting of 6 weeks.[12]

A weekly clinical assessment was scheduled for each patient to evaluate treatment response and monitor any potential side effects. Metabolic and biochemical parameters were measured at baseline and after completing the 28-day dexamethasone treatment course.

A total of 5 mL of venous blood was drawn from each patient and then divided into 2 portions, where 3 mL was collected in an EDTA tube for DNA analysis, while the remaining 2 mL was placed in a gel tube and sent for biochemical tests.

Liver function tests including the measurement of total bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were conducted using the COBAS 501 automated analyzer. In addition, metabolic parameters were also assessed including the levels of triglycerides (TG) and random blood sugar (RBS).

DNA was extracted using the salting-out method and stored at -20°C until further analysis. Quality control was performed by assessing purity through spectrophotometric analysis (260/280 ratio) and checking integrity via agarose gel electrophoresis.

Genotyping was conducted through PCR amplification for two polymorphisms using specific primers.

Figure I

PCR Amplification protocol

Steps	Temperature (°C)	Duration (min)	Cycles
Initial Denaturation	95	5 min	1
Denaturation	95	1 min	30
Annealing	64	30 sec	30
Extension	72	1 min	30
Final extension	72	10 min	1
Hold	4	∞	-

Figure II

Primer Sequences and Product Sizes

Target Genes	Product size	Direction	Primer Sequence (5' → 3')
N363S (rs56149945)	357bp	Forward	AGTACCTCTGGAGGACAGAT
		Reverse	GTCCATTCTTAAGAAACAGG
BCL1 (rs41423247)	418bp	Forward	TGCTGCCTTATTTGTAAATTCGT
		Reverse	AAGCTTAACAATTTTGGCCATC

The PCR products were first visualized on a 2.5% agarose gel, then purified using the Invitrogen Pure Link Quick Gel Extraction kit (Catalog Number K2100-12). After purification, the samples were sent for sequencing to Beijing TSINGKE Xinye Biotechnology Company.

Primary outcomes included evaluating the clinical manifestations of glucocorticoid treatment related side effects and association between polymorphisms of the GR gene (NR3C1) and these adverse effects.

Statistical analysis was performed using descriptive statistics to summarize demographic and clinical data. Pre- and post-treatment metabolic and biochemical parameters were compared using the Chi-square test, while the associations with polymorphisms were analyzed using Independent T-Test, Fisher's Exact Test and Chi-square test, whichever applicable.

A p-value of < 0.05 was considered statistically significant for all analyses.

RESULTS

The mean age of patients in this study was 12.56 ± 5.1 years with an age range of 6 months to 25 years. The sample consisted of 70.5% males and 29.5% females. The demographics and baseline clinical features of patients are shown in Table-I.

Table I

Demographics and baseline clinical features (n=88)

Demographics		
Age (Mean ±SD) Years		12.56 ± 5.1
Gender	Male n (%)	62 (70.5)
	Female n (%)	26 (29.5)
History of cousin marriage (%)		56 (63.33)
Clinical features		
Fever n (%)		88 (100)
Headache n (%)		54 (61)
Abdominal pain n (%)		52 (59)
Epistaxis n (%)		50 (57)
Blurred Vision n (%)		36 (41)
Gastritis n (%)		32 (36)

Comparison of Pre- and post-treatment incidences of metabolic, cardiovascular, and hepatic Complications showed that GC treatment significantly increased hyperglycemia ($p<0.001$), hypertension ($p=0.002$), hypertriglyceridemia ($p<0.001$), dyslipidemia ($p<0.001$), elevated ALT ($p=0.034$), elevated ALP ($p<0.001$), and Cushingoid features ($p<0.001$), while there was no significant change in raised bilirubin (0.223) as shown in Table-II.

Table II

Glucocorticoid-associated metabolic, cardiovascular, and hepatic complications (n=88)

Metabolic, cardiovascular, and hepatic variables	**Pre-treatment n (%)**	**Post-treatment n (%)**	**p-value***
Hyperglycemia (RBS >140 mg/dl)	5 (5.7)	15 (17)	<0.001
Hypertension**	4 (4.5)	12 (13.6)	0.002
Weight gain (>7% from baseline)	---	22 (25)	N/A
Hypertriglyceridemia (>150 mg/dL)	8 (9.1%)	18 (20.5%)	<0.001
Dyslipidemia***	7 (8)	16 (18.2)	<0.001
Raised Bilirubin (>1.2 mg/dL)	8 (9.1)	10 (11.4)	0.223
Elevated ALT (>40 IU/L)	12 (13.6)	25 (28.4)	0.034
Elevated ALP (>300 IU/L)	6 (6.8)	14 (15.9)	<0.001
Cushingoid features	0 (0)	19 (21.6)	<0.001

Chi-square test*, BP >95th percentile for age, sex, and height in children; >140/90 mmHg in adults**, Dyslipidemia defined as elevated triglycerides and/or total cholesterol >200 mg/dL ***

In genotype polymerization of 88 initial samples, 84 were successfully genotyped (95.5% success rate). The genotypic and allelic frequencies of the N363S (rs6195) and BcLI (rs41423247) polymorphisms in the NR3C1 gene were analyzed. The N363S polymorphism was rare with predominantly AA genotype (97.6%) and minimal G allele frequency (1.2%), while BcLI polymorphism showed higher variability with GG genotype being most common (64.3%) and G allele frequency of 76.2% as shown in Table-III.

Table III

Genotype and allele frequencies of NR3C1 polymorphisms (n=84)

Polymorphism	**Genotype**	**Frequency (%)**
N363S	AA	82 (97.6)
	AG	2 (2.4)
	GG	0 (0)
	Allele frequency A n (%)	83 (98.8)
	Allele frequency G n (%)	1 (1.2)
BcLI	CC	8 (9.5)
	CG	22 (26.2)
	GG	54 (64.3)
	Allele frequency C n (%)	20 (23.8)
	Allele frequency G n (%)	64 (76.2)

In N363S genotype analysis, hyperglycemia ($p=0.03$) and hypertension ($p=0.02$) showed significant associations, while weight gain ($p=0.07$), ALT ($p=0.65$), ALP ($p=0.86$), and bilirubin ($p=0.94$) demonstrated no significant associations, with notably all AG genotype carriers (n=2) developing hyperglycemia, weight gain, and hypertension as shown in Table-IV.

Table IV

Association of clinical and biochemical parameters with N363S genotype (n=84)

Clinical & biochemical parameters		N363S Genotype Association n (%)/(Mean±SD)	p-value
Hyperglycemia	AA (n=82)	13 (16)	0.03
	AG (n=2)	2 (100)	
Weight gain	AA (n=82)	20 (24.4)	0.07
	AG (n=2)	2 (100)	
Hypertension	AA (n=82)	10 (12.2)	0.02
	AG (n=2)	2 (100)	
ALT	AA (n=82)	39.2 ± 34.5	0.65**
	AG (n=2)	50.6 ± 33.9	
ALP	AA (n=82)	150.1 ± 64.2	0.86**
	AG (n=2)	158.4 ± 50.7	
Bilirubin	AA (n=82)	0.65 ± 0.92	0.94**
	AG (n=2)	0.70 ± 0.36	

*Fisher's Exact Test, Independent t-test**

None of the parameters showed significant associations with BcLI genotype, including hyperglycemia (p=0.82), weight gain (p=0.44), hypertension (p=0.56), ALT (p=0.33), ALP (p=0.63), and bilirubin (p=0.68), as shown in Table-V.

Table V

Association of clinical and biochemical parameters with BcLI genotype (n=84)

Clinical & biochemical parameters		BcLI Genotype Association n (%)/(Mean±SD)	p-value
Hyperglycemia	CC (n=8)	2 (25)	0.82*
	CG/GG (n=76)	13 (17)	
Weight gain	CC (n=8)	3 (37.5)	0.44*
	CG/GG (n=76)	19 (25)	
Hypertension	CC (n=8)	2 (25)	0.56*
	CG/GG (n=76)	10 (13.2)	
ALT	CC (n=8)	38.8 ± 33.2	0.33**
	CG/GG (n=76)	51.2 ± 34.1	
ALP	CC (n=8)	149.8 ± 63.1	0.63**
	CG/GG (n=76)	159.2 ± 51.3	
Bilirubin	CC (n=8)	0.64 ± 0.90	0.68**
	CG/GG (n=76)	0.71 ± 0.38	

* Chi-square test, Independent t-test**

DISCUSSION

The mean age of patients in our study was 12.56 ± 5.1 years with an age range of 6 months to 25 years. The sample consisted of 70.5% males and 29.5% females. GC treatment significantly increased the incidences of hyperglycemia (p<0.001), hypertension (p=0.002), hypertriglyceridemia (p<0.001), dyslipidemia (p<0.001), elevated ALT (p=0.034), elevated ALP (p<0.001), and Cushingoid features (p<0.001).

Similar results were reported in studies conducted previously to find the incidence of adverse events in ALL patients treated with CS. A study by Tsai et al. reported increased susceptibility to hyperglycemia, hypertension, dyslipidemia, osteonecrosis, myopathy, and neuropsychological effects in leukemia patients receiving GC treatment. Patients with older age, obesity, and preexisting glucose abnormalities had the amplified risks, where hyperglycemia peaked during the first week of treatment. Dexamethasone showed a higher risk than prednisone, highlighting the need for careful monitoring and tailored therapeutic approaches.[11] In a recent review published by Pourhassan H et al., the side effects of GCs in leukemia treatment was mentioned as hyperglycemia, myopathy, bone toxicities and neuropsychological issues. These effects are more pronounced with higher doses, prolonged use, and in older patients or children over 10 years. The use of dexamethasone was associated with a higher incidence of these side effects compared to prednisone.[13]

In our study, the N363S polymorphism was rare with predominantly AA genotype (97.6%) and minimal G allele frequency (1.2%), while BCL1 polymorphism showed higher variability with GG genotype being most common (64.3%) and G allele frequency of 76.2% N363S. Genotype analysis in our study showed significant associations of N363S polymorphism with hyperglycemia (0.03) and hypertension (0.02), while BcLI genotype showed no significant associations with any parameter. All AG genotype carriers (n=2) developed hyperglycemia, weight gain, and hypertension.

Namazi S et al performed a case-control study aimed to evaluate the association between three GR gene polymorphisms BcLI, N363S, and ER22/23EK, and the risk of relapse and the incidence of side effects. The percentage incidences of mutant allele BcLI was higher 19.5% compared to N363S (2.0%), and for ER22/23EK (0.5%). There was no statistically significant association reported between these genetic variations and GC-related side effects in this study.[14] The findings of Eipel O et al. were also similar to our results who examined the impact of glucocorticoid receptor SNPs (N363S, ER22/23EK, and BclI) on CS-related toxicities and survival in pediatric patients suffering from ALL. N363S carriers had higher risks of hepatotoxicity (P=0.004) and glucose abnormalities (P=0.001) but showed better 5-year survival rates (P<0.05). ER22/23EK carriers had fewer toxicities, while Bcl1 showed no significant associations.[15] The association of NR3C1 polymorphisms (BcLI, N363S, ER22/23EK) with glucocorticoid toxicity risks was worked by El-Fayoumi R et al. in 70 pediatric ALL patients versus 60 controls. The results showed that NR3C1 variants did not affect

ALL susceptibility. N363S carriers had higher toxicity (40% vs 6.51%, p=0.009) and glucose abnormalities (OR=10.167) while BcLI increased liver toxicity (OR=2.667) and glucose risks (OR=7.5). The polymorphism ER22/23EK was absent in these patients.[16]

Kaymak Cihan M et al. investigated the incidence of GC-induced side effects, the prevalence of N363S and BclI polymorphisms**,** and their association with treatment-related complications in pediatric ALL patients**.** The BclI polymorphism was common and linked to higher rates of dyspepsia, depression, and Cushingoid features**,** while no N363S polymorphism was detected in the study participants.**[17]** Reimondo G et al. also examined the association of NR3C1 polymorphisms (N363S and BcLI) with CS-induced side effects in ALL patients**.** The N363S polymorphism was significantly linked to hypertension (p=0.015), which suggest increased CS sensitivity. BcLI polymorphism, although, highly prevalent (54.7%) but showed no strong correlation with clinical outcomes. [18]

These findings of our study and studies discussed above suggest that polymorphism may influence the efficacy and adverse effects profile of GC in ALL patients and emphasized the need of genetic screening for personalized glucocorticoid therapy.

The limitations of our study include its small sample size. Moreover, this was a single-center study; future studies involving a larger sample and multiple research centers will further contribute to this useful data regarding the treatment of ALL patients.

CONCLUSION

Genetic screening may help to predict high-risk patients and enable personalized GC therapy in ALL management to reduce the metabolic, cardiovascular, and hepatic risks. As the data revealed from Khyber Pakhtunkhwa, Pakistan, BcLI polymorphism is more common, however, it shows weaker associations with treatment related side effects, while the N363S polymorphism is rare but found to be significantly associated with GC-induced metabolic complications, including hyperglycemia, hypertension, and weight gain**.**

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