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The relationship between GSH enzyme with risk of childhood acute lymphoblastic leukemia ALL

Maryam Isam Abdullah
Email: nassrymaryam@gmail.com
Department of Biology, Faculty of Science, University of Kufa, Iraq

Alaa Shakir Al-Nahi
Email: alaa.alnahi@uokufa.edu.iq
Department of Biology, Faculty of Science, University of Kufa, Iraq

Abstract---Total sample number 90 were 60 children diagnosed with Acute lymphoblastic leukemia (ALL) collect form Center Tumor cancer in Najaf , Warith international cancer institute in Karbala and select 30 children normal heath (control) from Amir al-Muminin Hospital and study conduct with molecular lab biology in the Department of Biology / Faculty of Science – University of Kufa, during the period from November 2021 to April 2022, The study demonstrated that there are highly significant differences in the enzyme GSH between those who carry the allele null in patients and control *GSTT1, GSTM1*and *GSTT1&GSTM1* (2.05±1.40 , 2.27±1.73,2.21±1.5) and (3.7±1.9, 3.2±1.8, 3.86±1.7) respectively , the allele present in patients and control *GSTT1, GSTM1*,and *GSTT1&GSTM1* (5.33±0.38 ,4.78±0.68, 5.03±0.7) , (10.64±1.7 , 9.73±2.7 , 9.9±2.5) respectively.

Keywords---GSH enzyme, childhood, acute, lymphoblastic, leukemia.

Introduction

Children are vulnerable to environmental toxins more than adults because of their relatively greater exposure, immature metabolism and higher levels of cell division and growth, Existence of an effective detoxifying enzyme system helps in the metabolism of potentially harmful environmental toxins to inactive metabolites thereby imparting protection from development of cancer (Huang *et al.*, 2013). GSTs superfamily is divided into seven classes, based on their structural, chemical, and physical properties: Alpha, Mu, Omega, Pi, Sigma, Theta, and Zeta. Genetic polymorphism in genes encoding these enzymes may interfere with their enzyme activity. *GSTM1* and *GSTT1* genes present insertion-deletion polymorphisms, and null allele implies the absence of enzyme activity.

Several studies found associations between *GSTM1/GSTT1* null genotypes and the risk of cancer in different populations (Anantharaman *et al.,* 2007*).*

Glutathione S-transferase (GST) M1, P1 and T1 are phase II enzymes involved in metabolism and detoxification of reactive ,oxygen species, xenobiotics and carcinogens Genetic variation in this gene family have been associated with increased susceptibility to certain primary as well as chemotherapy-induced second cancers, The genes encoding the enzymes *GSTM1* and *GSTT1* are polymorphic, and polymorphisms in these genes lead to decreased activity of the corresponding enzymes leading to increased susceptibility to environmental as well as other toxins, Null mutations in *GSTM1* and *GSTT1* lead to loss in the corresponding enzyme activity (Strange et al.,2001). GSTs catalyze the conjugation of reduced glutathione (GSH) to a wide variety of electrophilic compounds in order to make them more soluble enabling their elimination (Hollman *et al.*, 2016) GSH is involved in DNA synthesis and repair, In case of leukemia reduced levels of GSH reflects the depletion of non-enzymatic antioxidant reserve, It reflects that the GSH depletion, which normally acts as an antioxidant factor (Mohseni *et al.*, 2018). As a result of this detoxification activity, GSTs protect the cell from DNA damage, genomic instability and cancer development. In addition, as non-enzymatic proteins, GSTs can modulate signalling pathways that control cell proliferation, cell differentiation and apoptosis, among other processes (Dusinska *et al.*, 2012). Deletion polymorphisms of *GSTM1* and *GSTT1* genes and the single nucleotide polymorphism lead to the absence or reduced detoxification capacity of the enzyme. Differences in GSTs activity may modify the risk of cancer development and also may impact on the heterogeneous responses to toxic substances or specific therapies (Hollman *et al.*, 2016). Individual inherited genetic differences related to polymorphism in detoxification enzymes could be an important factor not only in carcinogen metabolism but also in cancer susceptibility (Yaya *et al.*, 2014).

Materials and Methods

In this study the patient group consist of 60 case of children diagnosed with Leukemia (ALL) and the matched healthy group (control) consist of 30 case with no Leukemia I was collect my sample from tumor center in Al-Najaf Patient who have confirmed diagnosis of (ALL) in children age (1.5 -7) years regard gender and ether group and attended cancer center.

Detection of Glutathione (GSH)

To quantify GSH levels, the BioVision GSH Assay Kit #K261 was used. This GSH Assay Kit #K261 utilizes a carefully optimized enzymatic recycling method, using glutathione reductase, for the quantification of GSH.

Statistical Analysis

Mega Stat. Xla statistical software program was used to describe patients' characteristics of mean, standard error, and percentage, ORs. Student's test and p-value were used and calculated for mean comparisons, $p \leq 0.05$ were

considered significant, in addition to that Microsoft Excel 2016 program was used.

Results

Childhood Leukaemia is a widespread cancer in pediatric age that differs from adult cancers in its nature. The disease is one of the biggest challenges regarding worldwide mortality and morbidity, and shows considerable variation in disease incidence across geographical regions (Al-absi *et al.,* 2017; Zheng *et al.,* 2017). Glutathione S-transferases are pivotal in maintaining cellular homeostasis by providing cytoprotection from environmental carcinogens, toxins, byproducts of oxidative stress and drugs. Additionally, cell signaling, post-translational modifications, cell proliferation, differentiation, cellular apoptosis, anti-inflammatory, proinflammatory, prevention of DNA damages, and resistance to chemotherapeutic drugs are other non–enzymatic function of GTs (Cerliani *et al* ., 2016; Singh *et al* ., 2021). *GSTT1* and *GSTM1* genetic polymorphisms are associated with loss–of–function mutations that leads to the complete loss of activities of these enzymes (Baba *et al*., 2021). Most of these finding was compatible with recent studies of (Abdalhabib *et al* ., 2022 ; Moulik *et al* ., 2014) Multiple studies have demonstrated that susceptibility to cancer is caused by a deficiency in xenobiotic-metabolism genes (*GSTT1* and *GSTM1*)were significantly higher in the cases groups compared to the control group (Aziz, 2010) data demonstrated that GST frequent determined in Iraq population GST polymorphism have been related to different cancer some of may be direct associated with cancerogenic toxic factor.

Table 1
Show Relation of GSH enzyme with GST polymorphism in control

Genotype	GSH µM		P-value
	Null (no.) mean ±SD	present (no.) mean ±SD	
GSTT1	3.7 ± 1.9	10.64 ± 1.7	0.000
GSTM1	3.2 ± 1.8	9.73 ± 2.7	0.001
GSTT1 & *GSTM1*	3.86 ± 1.7	9.9 ± 2.5	0.00

Values are expressed as mean ±SD, and the different letters significant difference at p-value 0.05 control n=30

Table 2
Relation of GSH enzyme with GST polymorphism in patient

Genotype	GSH µM		P-value
	Null mean ±SD	Present mean ±SD	
GSTT1	2.05 ± 1.40	5.33 ± 0.38	0.001
GSTM1	2.27 ± 1.73	4.78 ± 0.68	0.002
GSTT1 & *GSTM1*	2.21 ± 1.5	5.03 ± 0.7	0.000

Values are expressed as mean ±SD, and the different letters significant difference at p-value 0.05 patient n=60

Our results indicated that antioxidant enzyme (GSH) was significantly lower in patients with null genotype than in present for both *GSTT1*, *GSTM1* and *GSTT1/GSTM1* genotype polymorphisms in ALL (2.05 ± 1.40 , 2.27 ± 1.73 **,** 2.21 ± 1.5) µM respectively, (p=0.0001) (Table 1, 2). These results are in agreement with findings by (Asmat *et al.*, 2016), among the genotypes, the null *GSTM1/GSTT1* group had the least GSH expression levels pointing toward the additive effect of these deletions, Testa and Labbaye, (2016). The protect cells against oxidative stress by increasing the intracellular glutathione (GSH) because that the GSH is working as a co-enzyme for many enzymes which responsible for protect the cells from damage caused by oxidation compounds and support their growth and survival (Reehan *et al.*, 2018). Hereditary differences in the expression and activity of human GSTs have been reported, and altered GST enzymatic activity is associated with different types of cancer (Karaca *et al.,* 2015). GSTs have the ability to modulate the non-enzymatic proteins and signalling pathways that control cell proliferation, differentiation, and apoptosis (Cameron *et al.,* 2021). Various types of GSTs translate internal and external carcinogenic compounds and ROS to non-toxic substances. *GSTM1* and *GSTT1* null are considered loss of function mutations as they involve the loss of structural homozygosity and predominantly lead to loss in the corresponding enzyme activity (Moulik *et al* ., 2014). The association of GST polymorphisms and childhood ALL was in 1997 by Chen *et al* first reported the linkage between *GSTT1* polymorphism and incidence of childhood acute leukemia among both black and white children.(Ma *et al* ., 2019). The generation of reactive oxygen species (ROS) and other free radicals during metabolism is a necessary and normal process that ideally is compensated for by an elaborate endogenous antioxidant system However, due to many environmental, lifestyle, and pathological situations, excess radicals can accumulate, resulting in oxidative stress Oxidative stress has been related to cardiovascular disease, cancer, and other chronic diseases that account for a major portion of deaths today (Safitri *et al.,* 2018).

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