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HIF-1α and ENPP2 as Biomarkers in Chemotherapy Resistance of Children with Neuroblastoma in south Iraq

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Abstract

Background: The most common extra-cranial solid tumor in kids, Neuroblastoma (NB) accounts for 10% of all pediatric oncology fatalities. It emerges in the embryonic neural crest due to the uncontrolled behavior of sympathetic nervous system progenitors, giving rise to heterogeneous tumors. Although immunotherapy and targeted therapy have advanced quickly, surgery, chemotherapy, and radiation (RT) still make up the majority of first-line options for treating cancer. Recurrence of the illness and diminished efficacy of chemotherapy and RT are among the factors that contribute to treatment failure. This study was aimed at evaluating the effects HIF-1α, ENPP2 and oxidant / antioxidant of chemotherapy resistance with NB children.

Methods: This study extended from May 2022 to end of March 2023, with age range 2 months to 12 years. 70 children (male/ female) were divided into three groups. Group A: includes 35 healthy children as control group, and group B: includes 35 patients of Newly diagnosed and group C: after three cycles of chemotherapy. Detailed information regarding the age and gender was recorded for every participant.

Results: The present study's findings showed a considerable rise in ($p<0.05$) at the levels of HIF-1α, MDA, ENPP2 while the outcomes showed a statistically significant decrease ($p<0.05$) at the levels of GSH, in the sera samples of patients with NB (pre-treatment) when compared to the control group. The findings, on the other hand, demonstrate that each of the following parameters—HIF-1, MDA, and GSH—decreased in levels in NB patients after receiving chemotherapy dosages. Nevertheless, following therapy, ENPP2 levels increased.

Conclusion: Our findings are indicative of the fact that early diagnosis plays an important role in the effectiveness of chemotherapy. and the levels of oxidant- anti oxidant status, HIF-1α and ENPP2 are significant features of the monitoring of disease progression and the efficacy of treatment.

Introduction

Neuroblastoma (NB), which manifests in childhood as an extra-cranial solid tumor of the sympathetic nervous system, accounts for 15% of pediatric cancer mortality [1]. NB is the second most common extra-cranial malignant tumor in children, accounting for 8% to 10% of all pediatric malignancies [2]. Though the majority of NB tumors arise sporadically, this cancer is rarely heritable [3]. Male patients are afflicted more commonly than female patients, and the majority of children are diagnosed before the age of five [4]. A variety of biological processes, including cell proliferation, cell survival, and cell invasion, are dysregulated in the intratumoral microenvironment due to hypoxia, which often leads to tumor aggressiveness and treatment resistance [5]. Hypoxia is a prominent characteristic of solid tumors and is thought to be a frequent cause of poor patient prognosis and therapeutic outcomes [6]. A transcription factor known as hypoxia-inducible factor 1 alpha (HIF-1), HIF-1 is often stable and active in hypoxic conditions [5]. Hypoxic cells paradoxically increase their mitochondrial production of reactive oxygen species (ROS), leading to oxidative stress [7]. Oxidative stress (OS) is characterized as an imbalance between oxidants and antioxidants, as well as an excess of reactive oxygen species (ROS)[8]. ROS has two opposing effects: low levels of ROS are an essential signaling molecule in many pathophysiologic processes, whereas high levels of ROS destroy cellular components and start cell death [9]. ROS production impact on membrane to suffer from lipid peroxidation and produce Malondialdehyde (MDA) as membrane damages intermediate [10]. MDA is the most often utilized marker to assess the existence of oxidative stress in biological systems [11]. MDA is a compound with a high biological activity and is cytotoxic, mutagenic, and carcinogenic. Additionally, this tricarbon aldehyde may have an impact somewhere outside where it originated. It can damage cells both inside and outside by migrating across cellular membranes [12]. The body's fight against free radicals depends heavily on antioxidants [13]. Glutathione (GSH), which is a key component of many metabolic activities in addition to antioxidant defense systems, is one of the enzymatic systems that contributes to the maintenance of the intracellular redox equilibrium [14]. Numerous cell types have been shown to benefit from GSH's ability to prevent the development of apoptosis and necrotic cell death [15]. GSH system's is crucial for defending neurons against damage caused by impaired energy metabolism [16]. Due to the GSH system's intricate physiological makeup, its disequilibrium is implicated in a number of pathogenic pathways and thus plays an important role in cancer. It is also crucial for controlling the progression through the cell cycle as well as cell survival, growth, and death [17]. Evidence points to autotaxin (ATX) and lysophosphatidic acid receptors (LPARs) being involved in the promotion of cancer cell invasion by the hypoxic tumor microenvironment [18]. Ectonucleotide pyrophosphatase 2 (ENPP2), also known as autotaxin (ATX) [19], ENPP2 is expressed in a variety of tissues, with high levels in the brain and adipose tissue. It is also present in a variety of biological fluids, with high concentrations in blood and serum [20]. The human chromosomal region 8q24, where ENPP2 is found, frequently experiences genetic changes in many cancers [21]. The reason for our conducting this study is due to the prevalence of childhood cancer in the southern region of Iraq, especially Basra Governorate, due to environmental pollution resulting from the burning of oil and other pollutants, in addition to the remnants of war. Moreover, due to the lack of studies that study solid tumors, especially Neuroblastoma. Therefore, this study was conducted to find out the changes that the tumor may cause in the body and the effect of chemotherapy after three cycles of treatment on MDA, GSH, ENPP2, and HIF in Neuroblastoma patients.

Methods

Seventy research participants were included in the current study during the prolonged period from May 2022's first day to March 2023's last day. 35 samples of Newly diagnosed with NB in Al-Basra Children Teaching Specialty Hospital in Basra Governorate, south Iraq. Their age ranged between from two months to 12 years old. 70 children (male/ female) were divided into three groups. Group A: includes 35 healthy children as control group, and group B: includes 35 patients of Newly diagnosed and group C: after three cycles of chemotherapy (after the 9th week of treatment, the same patients who were diagnosed). Specialists used clinical methods to make an early diagnosis and performed routine blood testing on patients. Written informed consent was obtained from the sick children's parents.

Each group (controls and patients) had 6 mL of blood drawn. Samples were centrifuged at 3000 x g for 10 minutes after being allowed to coagulate at room temperature in empty disposable tubes. If not used right away, isolated serum samples were kept at -20 °C for further assessment of biochemical parameters.

HIF-1, ENPP2, and GSH were measured in the blood using an ELISA (enzyme linked immunosorbent assay). Using a modified version of Fong et al.'s [22] colorimetric approach, malondialdehyde (MDA) activity was quantified as thiobarbituric acid (TBA) activity.

Patients with diabetes and autism disorders were excluded.

Using the SPSS version 23 software, the statistical analysis findings of the statistical analysis have been presented as the mean and standard deviation (mean ± SD). For comparing the subgroups, a one-way ANOVA was used. Using Pearson's correlation, it was determined that the parameters of the current study were related. P-values (P 0.05) have been used to determine when there is a statistically significant difference.

Results

Table (1) provides a summary of the general characteristics of the children who took part in the study, which include the following details on age and gender, and place of residence:

Clinical Characteristics	Percentage	
Age Group	2 M - 1Y	5 (14.3 %)
	2Y – 5Y	17 (48.6 %)
	6Y – 12Y	13 (37.1 %)
Gender	Male	22 (63 %)
	Female	13 (37 %)
Total	……	35 (100 %)

Where M: Month, Y: Year.

Table 1: The age and gender of the studied groups

Table (2) shows a significant increase in the concentration of HIF-1A in B group in comparison with A and C groups (p≤0.05). It was found that a significant increase in the concentration of HIF-1A in C group in comparison with A group (p≤0.05).

Groups	No.	HIF1α (ng/dL) (Mean ±SD)
A	35	26.01± 4.76 [c]
B	35	57.60± 7.47 [a]
C	35	48.25± 9.16 [b]
L.S.D		2.92

A: control, B: Before chemotherapy , C: after chemotherapy. SD represents the Standard deviation. No represents the Number of subjects. LSD represents the Least Significant Difference (a, b, c) indicates having various letters in same column have been significantly differed (p <0.050).

Table 2: Levels of serum HIF-1α in patient and control groups

Table (3) shows a significant increase in the concentration of MDA in B group in comparison with A and C groups (p≤0.05). It was found that a significant increase in the concentration of MDA in C group in comparison with A group (p≤0.05).

Groups	No.	MDA (µmol/L) (Mean ±SD)
A	35	1.26± 0.26 [c]
B	35	3.38±0.80 [a]
C	35	2.81±1.08 [b]
L.S.D		0.24

A: control, B: Before chemotherapy , C: after chemotherapy. SD represents the Standard deviation. No represents the Number of subjects. LSD represents the Least Significant Difference (a, b, c) indicates having various letters in same column have been significantly differed (p <0.050).

Table 3: Levels of serum MDA in patient and control groups

Table (4) shows a significant decrease in the concentration of GSH in C group in comparison with A and B groups (p≤0.05). It was found that a significant decrease in the concentration of GSH in B group in comparison with A group (p≤0.05).

Groups	No.	GSH (Ug/mL) (Mean ±SD)
A	35	2.68±0 .71 [a]
B	35	1.70± 0.40 [b]
C	35	0.57±0.17 [c]
L.S.D		0.19

A: control, B: Before chemotherapy , C: after chemotherapy. SD represents the Standard deviation. No represents the Number of subjects. LSD represents the Least Significant Difference (a, b, c) indicates having various letters in same column have been significantly differed (p <0.050).

Table 4: Levels of serum GSH in patient and control groups

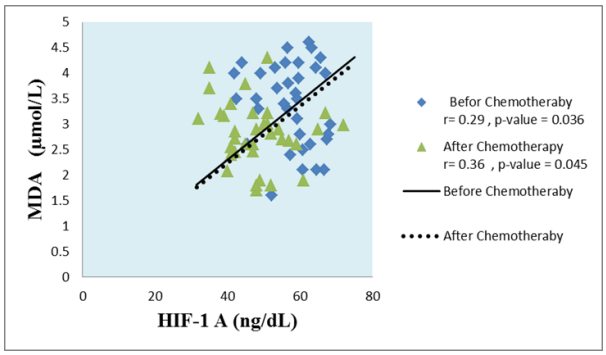
Table (5) shows a significant increase in the concentration of ENPP2 in C group in comparison with A and B groups (p≤0.05). It was found that a significant increase in the concentration of ENPP2 in B group in comparison with A group (p≤0.05).

Groups	No.	ENPP2 (ng/dL) (Mean ±SD)
A	35	22.80± 4.52 [c]
B	35	75.84±7.24 [b]
C	35	86.04±10.10 [a]
L.S.D		2.89

A: control, B: Before chemotherapy , C: after chemotherapy. SD represents the Standard deviation. No represents the Number of subjects. LSD represents the Least Significant Difference (a, b, c) indicates having various letters in same column have been significantly differed (p <0.050).

Table 5: Levels of serum ENPP2 in patient and control groups

There is a positive correlation between HIF-1A and MDA levels in each of before chemotherapy (r = 0.29), after chemotherapy (r= 0.36) as shown in figure(1).



r=0 represents no correlations 0< r<0.250 represents weak extreme 0.25<r<0.75 denotes the moderate extreme 0.75<r<1 represents the strong extreme r=1 represents the Perfect value.

Figure 1: Correlation between serum HIF-1α and MDA in patient Groups.

There is a negative correlation between HIF-1α and GSH levels in each of before chemotherapy (r = - 0.41) and after chemotherapy (r = - 0.44) as shown in figure (2).

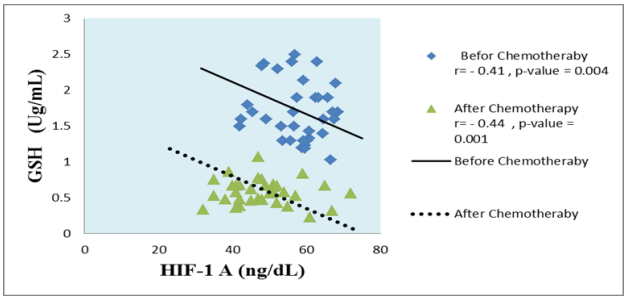


Figure 2: Correlation between serum HIF-1α and GSH in patient Groups.

There is a positive correlation between HIF-1A and ENPP2 levels in each of before chemotherapy (r = 0.33), after chemotherapy (r= 0.46) as shown in figure (3).

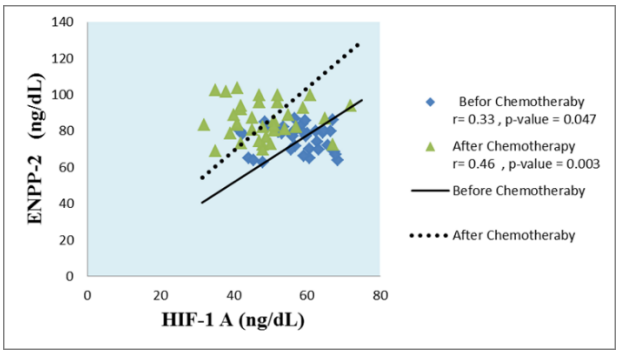


Figure 3: Correlation between serum HIF-1α and ENPP2 in patient Groups.

Discussion

The aggressive childhood tumor known as NB derives from the periphery neural crest [1]. Solid tumors frequently exhibit hypoxia because they are less well-oxygenated than healthy tissues [23]. The transcription factor HIF-1, which is triggered by hypoxia, has two subunits: HIF-1α and HIF-1β [24]. Generally speaking, conventional chemo-radio therapeutic regimens cannot completely destroy cancer cells. The improvement of cancer patients' long-term survival is frequently hampered by drug resistance and cancer recurrence [25]. According to Zhao et al research on treatment resistance, chemo-radiotherapy can cause cell apoptosis, which is thought to be a key mechanism in chemo-radiotherapy-induced cell death. Accordingly, Zhao et al. contend that apoptosis impairment is a major contributor to chemo-radio resistance and that apoptosis activation is dependent on different signaling pathways, namely the extrinsic route and the intrinsic pathway [26]. Depending on the period of the therapy, participants in this research were split into two groups. Before and after the chemotherapy treatment, the blood levels of (HIF-1α, MDA, GSH, and ENPP2) as well as a few symptoms and indicators were examined in the current investigation. Evidence points to hypoxia as a characteristic of NB, which affects treatment outcomes and activation of the HIF-1α pathway that leads to drug resistance [27]. HIF-1α has been associated with a poor prognosis in NB, and the current investigation found that NB had much higher blood levels of HIF-1α before treatment than did healthy individuals. Indicating that, this parameter is a marker of malignancy. This may be due to tissue necrosis occurring in tumor tissues with high HIF-1α protein expression, which allowed significant amounts of HIF-1α to reach the circulation [28]. Since hypoxia is directly related to chemo- radio resistance, we investigated at the levels of HIF-1α in patients following the third round of chemotherapy and discovered that the levels of HIF-1α dropped throughout chemotherapy. Reduced HIF-1 levels following the initiation of chemotherapy may help determine how effective it will be. The significant changes in the MDA level were found in NB cancer patients. It appears to be because of the potential for free radical accumulation, which manifests as noticeably greater lipid peroxidation Compared to the control subjects. While the level of MDA was much lower following treatment compared to the patients before chemotherapy. It might be explained by a decrease in oxidative stress caused by the chemotherapy-induced shrinkage of the tumor. According to our research, diagnosed NB patients had statistically lower levels of glutathione (GSH) before starting therapy than healthy controls. Additionally, GSH decreased more with chemotherapy as compared to NB patients and the healthy control group. This study supports the notion that oxidative stress persists in NB by suggesting a potential connection between lower GSH and increasing levels of cell changes brought on by oxidative damage. Due to the high quantities of H_2O_2 and other peroxides generated in tumor cells, the drop in thiol levels may signify a depletion of this antioxidant. Thiol levels are therefore not present in adequate quantities to protect the afflicted cells from oxidative stress [29]. Glutathione acts as the first line of defense against free radicals produced by antitumor chemicals. Decreased GSH levels can be explained by a reduction in GSH synthesis and/or an increase in GSH consumption for the removal of xenobiotics and peroxides [30]. Chemotherapeutic drug detoxification is significantly aided by GSH [31]. Before starting therapy, diagnosed NB patients had significantly higher ENPP2 (ATX) levels than control group. Activated oncogenes, a number of growth factors, and LPA can all cause HIF-1α production under nonhypoxic conditions, though HIF-1α is a transcription factor that regulates adaptive responses to variations in tissue oxygenation [32]. In solid tumors, overexpression of ENPP2 enhances tumor progression, angiogenesis, and treatment

resistance. ENPP2 has been found to play important roles in different pathophysiological processes, including inflammation, angiogenesis, fibrosis, and carcinogenesis [33]. While, there was statistically significant increase between ENPP2 levels after 3 cycle chemotherapy as compared to before chemotherapy. Indicating that, this parameter is also marker of malignancy. ENPP2 expression in cancer cells has been found to be induced by chemotherapy and radiation therapy and it has been identified as one of 90 genes linked to drug resistance in malignancies [34]. The current study reviews the current understanding of how activation of the ATX-LPA-inflammatory cycle promotes tumor growth as well as reduces the effectiveness of various chemotherapies used to treat NB. ATX from the surrounding cells in the tumor microenvironment produce the majority of LPA, which promotes cancer cell therapy resistance and spread. The majority of contemporary chemotherapy regimens directly target the cancer cell, yet acquired treatment resistance continues to be a significant clinical hurdle. This failure is primarily caused by the microenvironment's healing inflammatory milieu, which is neither inhibited or suppressed during therapy [34]. Numerous chemotherapy drugs, such as vincristine and doxorubicin (Adriamycin), as well as radiation treatment promote cell death by increasing ceramide production [35]. Sphingolipids called ceramides are easily transformed into sphingosine by ceramidases and subsequently into S1P by sphingosine kinase-1 (SK-1). Ceramides trigger caspases and release cytochrome C from the mitochondria to start apoptosis [36]. LPA and S1P, on the other hand, counteract ceramides' inhibitory effects on cell division. Ceramide and S1P concentrations in balance with their respective signals are thought to be a key "rheostat" that regulates whether cancer cells will die or survive [34].

The ATX/LPA axis appears, to play a significant role in NB, and inhibiting this signaling through the inhibition of ATX, blocking of LPAR, or downstream signaling might be a potent therapeutic, approach or could be used as an adjuvant therapy, to increase the effectiveness, of conventional anti-cancer treatment.

Author Contributions

All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Competing Interests

The authors declared that there were no conflictsof interest.

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