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Study of Epstein Barr virus, Human Herpes 6 and Human Herpes 7 in Children with Acute Lymphoblastic Leukemia

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A B S T R A C T

The aim of the present study is to identify the presence of Epestein Barr virus (EBV), Human Herpes virus 6 (HHV6)and Human Herpes virus 7 (HHV7) by molecular methods in newly diagnosed ALL in children and to correlate their presence with clinical and immunophenotypes of ALL. The present study included 60 children at the time of diagnosis of ALL before start of the therapy and 60 healthy cross match age and sex children as a control group. The study of EBV, HHC6 and HHV7 was carried out by real time polymerase chain reaction (PCR). In comparison between the prevalence of EBV, HHV6, HHV7 between patients and control there was statistically significant increase in prevalence rates (31.7 versus 1.7 for EBV, 16.7% versus 3.3% for HHV6 and 13.3% versus 8.3% for HHV7 respectively, P=0.0001). Moreover, the mean± SD copies/ml was statistically significant higher for HHV6 in patients compared to the controls (P=0.0001). There was significant association between EBV and HHV6 infection in patients (P=0.001). In EBV+ ALL, there was significant higher rates of hepatosplenomegaly (47.4%, P=0.01) In conclusion, EBV, HHV6 and HHV7 viruses were present in high rates in ALL which suggest a role for these viruses in pathogenesis of ALL. Further studies are required to validate this hypothesis.

Introduction

Acute lymphoblastic leukemia (ALL) is a global health burden especially in children. It represents a common malignancy of childhood. There are many new therapies that have been developed and there is a marked improvement of its outcome with around 68.2% five years survival. However, its pathogenesis remains a puzzle that needs to be resolved to be able to reduce its incidence. Among factors that may be associated with development of ALL are infectious agents. The infectious etiology of development of ALL is based upon two theories. The first one is associated with direct oncogenic mechanism due to expression of viral oncogenes and down regulation of tumor suppressor genes leading to cellular transformation [1, 2]. The other mechanism of oncogenesis due to infection claims the inflammatory reactions associated with infections that leads to immunosuppression with loss of immune surveillance mechanisms

or/and production of dome mutated products that lead to development of ALL [3]. The first mechanism of infectious agents associated with ALL is thought to act within the cells and leads to clonal expansion with the infectious particles carried in all expanded tumor cells[4]. The example for the first theory of infections associated with ALL are latent viral infections associated with herpes viruses such as human Herpes virus 6 (HHV6), human Herpes virus 7 (HHV7) and Epstein barr (EBV) virus.

Epstein barr virus is very common around the world infecting about 89% of the children and around 90% of the adults[5].The common cellular target of EBV virus is B lymphocytes with persistence of the virus in memory cells [6], however, there is growing evidences support that it may also infects T lymphocytes and natural killer cells with long persistent latent infection. The association of EBV with malignancy is well known with varieties of malignancies such as Burkitt's lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinoma [7].

The other viruses that are claimed to be associated with oncogenesis are human HHV6, and HHV7. These viruses infect young children with mild clinical signs such as fever and exanthema subitum HHV6 with complete cure and development of persistent and infection[8]. The persistence of herpes viruses occurs usually in salivary gland and mononuclear cells in the blood. The reactivation usually occurs in immune compromised conditions leading to severe infections such as encephalitis and retinitis [9]. The presence of high viral load with children with ALL was previously described [10].

The aim of the present study is to identify the presence of EB, HHV6 and HHV7 by molecular methods in newly diagnosed ALL in children and to correlate their presence with clinical and immune phenotypes of ALL.

Materials and Methods

The present study included 60 children at the time of diagnosis of ALL before start of the therapy from Mansoura Oncology centre, Egypt from March 2015 till January 2018.In addition to 60 healthy children were included as control group with no hematological disorders and with similar sex and age distribution. Children with other hematological malignancies or who started the therapy were excluded. The diagnosis of ALL was performed according to WHO 2008 criteria was established on the basis of the latest diagnostic criteria of WHO2008, including morphology and immune phenotypic markers for B-ALL and TALL[11]. The used markers for diagnosis of B-ALL were cCD3, CD2, CD5, CD7, CD8 and the used markers for T-ALL were cCD79, CD10, CD19, CD20, CD22.

The study was approved by Mansoura Faculty of Medicine ethical committee. Approval consents were obtained from the parents of all children.

Each child was subjected to full clinical examination and routine laboratory investigations. Seven milliliter of blood was obtained from each child over EDTA and plasma was separated and DNA was extracted and kept frozen at -20ºC until time of amplification.

DNA extraction

DNA was extracted from plasma samples by the use of QI Aamp DNA blood kits (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Quantification of viral DNA by multiplex real-time PCR for HHV6 and HHV7

Multiplex real time PCR was used to amplify and quantitate HHV6 and HHV7 according to the protocol developed previously [12].

The amplification mixtures used was supplied by Qiagen. Real-time PCR system and the following protocol: an initial denaturation and polymerase activation step for 15 min at95◦C, followed by 50 cycles of denaturation at 94◦C for60 sec and 62◦C for 90 sec. Real-time fluorescent measurements were recorded and a Ct value for each sample was calculated by determining the point at which the fluorescence exceeded the threshold. Each real-time PCR assay contained a standard dilution series for DNA quantification, and all samples were analyzed in duplicate. Negative controls were added to each run. The standards were plasmid controls that contained the PCR products amplified by each primer set as described previously. For multiplex real-time PCR, each plasmid control was mixed and diluted to produce standard curves. The number of viral DNA copies was calculated from these standard curves and expressed as copies/ml.

EBV by Real-time PCR

The amplification and quantitation of EBV was performed by real time PCR as previously described [13].

The used primers and probes were summarized in table 1.

Statistical analysis

Statistical package for social science program version 24 used for analysis. The quantitative data were presented as mean, standard deviations and ranges. The comparison between the studied groups was done by using One Way Analysis of Variance (ANOVA). P was considered significant<0.05

Results and Discussion

The study included 60 children with ALL their mean age± SD were 4.7 ±3.4 years mainly of male gender (73.3%). The main clinical signs were mucositis (35%), fever (31.7%), lymphadenopathy (31.7%) and hepatosplenomegaly (25%). The majority of the type of ALL was B-ALL (53.3%) (Table 2).

In comparison between the prevalence of EBV, HHV6, HHV7 between patients and control there was statistically significant increase in prevalence rates (31.7 versus 1.7 for EBV, 16.7% versus 3.3% for HHV6 and 13.3% versus 8.3% for HHV7 respectively, P=0.0001). Moreover, the mean± SD copies/ml was statistically significant higher for HHV6 in patients compared to the controls (P=0.0001) (Table 3).

There was significant association between EBV and HHV6 infection in patients (P=0.001) (Figure 1). There was increase in the prevalence of EBV (36.8%), HHV6 (40%) and HHV7 (75%) in age above 4 years, however the increase were insignificant (P=0.3, P=0.9, P=0.1 respectively) (Table 4).

In the comparison between children with ALL positive for EBV to those negative for EBV, there was significant predominance of male gender (98.5%, P=0.05)

In EBV+ ALL, there was significant higher rates of hepatosplenomegaly (47.4%, P=0.01), with significant increase of total leucocytes counts (mean± SD 46.5± 38.5, P=0.04) and absolute lymphocytosis (mean± SD 38.8± 3,2, P=0.02). There was significant association between B-ALL and EBV (89.5%, P=0.0001) (Table 5).

In comparison between children with ALL positive for HHV6 and negative for HHV6 the only significant clinical sign was hepatosplenomegaly (80%, P=0.0001) (Table 6).

In comparison between children with ALL positive for HHV7 and negative for HHV7, the positive children were significantly older

in age (mean± SD, 7.7± 2.6, P=0.0001) with significant reduction in hemoglobin level (mean± SD, 7.7± 2.6, P=0.0001) (Table 7).

EBV, HHV6 and HHV7 are known latent viruses with persistence lifelong after primary infections. Though, primary infections may passed unnoticed the persistent infections are linked to development of many types of malignancy. In the last few years there are significant links between the presence of EBV and development of leukemia [14].

In the present study EBV-DNA was present in 31.7% of the children with ALL versus 1.7 for EBV-DNA in control children. Similar results were reported for presence of active EBV associated with leukemia in Egypt either by use of serological markers [15, 16] and were online with other studies from different geographical regions [17, 18]. The low prevalence of EBV viremia in the control subjects compared to study by Loutfy *et al.*, 2006[15] may be attributed to the difference of the laboratory methods used in both studies. The presence of serological markers of EBV in control subjects are not always indicators of acute EBV infection and even the presence of positive serological markers of EBV are not always present in active infection in immune compromised patients such as ALL.

EBV belongs to herpes virus family and its activation is known to be a nosogenesis of malignant diseases[2]. It is well known that EBV leads to chromosome mutations and translocation in lymphocytes that lead to c-myc oncogene activation and excessive expression[19]. However, the exact mechanisms associated with development of lymphoproliferative disorders associated with EBV need further extensive studies

Table.1 Viruses and the sequences of the used primers and probes

Virus	Primers and probes sequences
EPV	**F: 5'-CCCAACACTCCACCACACC-3'** **R: 5'-TCTTAGGAGCTGTCCGAGGG-3'** **5'-CACACACTACACACACCCACCCGTCTC-3'.**
HHV6	**5'-TTTGCAGTCATCACGATCGG-3'** **5'-AGAGCGACAAATTGGAGGTTTC-3'** **Probe5'-AGCCACAGCAGCCATCTACATCTGTCAA-3'**
HHV7	**F:5'-CGGAAGTCACTGGAGTAATGACAA-3'** **R: 5'- ATGCTTTAAACATCCTTTCTTTCGG-3'** **Probe 5'-CTCGCAGATTGCTTGTTGGCCATG-3'**

Table.2 Demographic, clinical and laboratory data of children with ALL

Sex **Male** **Female**	 44 73.3% 16 26.7%
Age	 4.7±3.4 0.5 13.5
Fever	19 31.7%
Hepatosplenomegaly	15 25%
Lymphadenopathy	19 31.7%
mucositis	21 35%
Total leucocytic counts x $10^3/mm^3$ **Median** **Minimum** **Maximum**	 10.000 1.30 154.00
HB g/dl	8.1± 2.6 3.1 11.00
RBCsx10^6/l	3.7± 0.9
Platelets x $10^3/mm^3$	 52.3± 39.3 9.2 188.000
Neutrophil x $10^3/mm^3$	3.03± 2.00 0.8 10.000
Lymphocytes x $10^3/mm^3$ **Median** **Minimum** **Maximum**	 9.7 0.6 130.00
Type of ALL **B-ALL** **T-ALL**	 32 53.3% 28 46.7%

Table.3 Comparison of EBV, HHV6, HHV7 between patients and control

	Patients	**Control**	**P**
EBV-DNA **Mean± SD** **(copies/ml)**	19 31.7% 9333± 1581.1	1 1.7% 7000	P=0.0001
HHV6 **Mean± SD** **(copies/ml)**	10 16.7% 514± 25	2 3.3% 505± 21.0	P=0.0001
HHV7 **Mean± SD** **(copies/ml)**	8 13.3% 505± 12.9	5 8.3% 420± 81.5	P=0.0001 P=0.1

Table.4 Prevalence of EBV, HHV6 and HHV7 in patients according to age

	0-2 years **N0. %**	**<2-4 years** **N0. %**	**>4 years**	**P**
EBV (n=19)	6 31.6%	6 31.6%	7 36.8%	P=0.3
HHV6 (n=10)	2 20%	4 40%	4 40%	P=0.9
HHV7 (n=8)	2 25%	0 0%	6 75%	P=0.1

Table.5 Comparison between EBV positive and EBV negative patients

	EBV+ **(n=19)** **No. %**	**EBV-** **(n=41)** **No. %**	**P**
Sex **Male** **Female**	 17 89.5% 2 10.5%	 27 65.8% 14 34.2%	 P=0.05
Age	5.00± 3.7	3.9± 2.5	P=0.3
Fever	12 63.2%	7 17.1%	P=0.4
Hepatomegaly	9 47.4%	6 14.6%	P=0.01
Lymphadenopathy	12 63.2%	7 17.1%	P=0.4
Mucositis	14 34.1%	7 17.1%	P=0.5
Total leucocytic counts x 10^3/mm^3	46.5± 38.5	17.7± 14.7	P=0.04
HB g/dl	8.0± 2.6	8.1± 2.6	P=0.9
RBCsx10^6/l	3.7± 1.0	3.7± 0.8	P=0.9
Platelets x 10^3/mm^3	48.3± 35.8	52.2± 41.14	P=0.6
Neutrophils x 10^3/mm^3	2.9± 1.5	3.3± 2.7	P=0.5
Lymphocytes x 10^3/mm^3	38.8± 3.2	13.4± 10.6	P=0.02
Type of ALL **B-ALL** **T-ALL**	 17 89.5% 2 10.5%	 15 36.6% 26 63.4%	 P=0.0001

NB: EBV+: EBV positive
EBV-: EBV negative

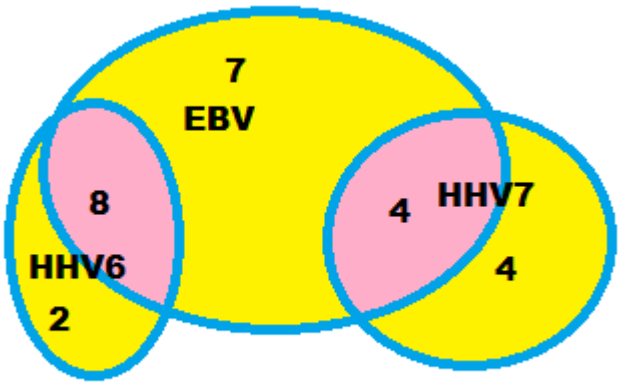
Table.6 Comparison between HHV6 positive and HHV6 negative patients

	HHV6+ (n=10)	**HHV6- (n=50)**	
Sex **Male** **Female**	 8 80% 2 20%	 36 72% 14 28%	P=0.5
Age	4.6 2.1	4.6 3.6	P=0.9
Fever	4 40%	15 30%	P=0.4
Hepatosplenomeegaly	8 80%	7 46.7%	P=0.0001
Lymphadenopathy	5 50%	13 26%	P=0.04
mucositis	2 20%	19 38%	P=0.2
Total leucocytic counts x $10^3/mm^3$	18.4 13.0	44.3 33.5	P=0.3
HB g/dl	7.5± 2.1	8.2± 2.7	P=0.4
RBCsx10^6/l	3.5± 0.7	3.7± 0.9	P=0.2
Platelets x $10^3/mm^3$	48.04± 30.04	53.1± 41.1	P=0.7
Neutrophils x $10^3/mm^3$	2.7± 1.7	3.1± 2.02	P=0.5
Lymphocytes x $10^3/mm^3$	15.04± 11.9	37.03± 27.5	P=0.3
Type **B-ALL** **T-ALL**	 8 80% 2 20%	 24 48% 26 52%	P=0.4

Table.7 Comparison between HHV7 positive and HHV7 negative patients

	HHV7+ (n=8)	**HHV7- (n=52)**	
Sex **Male** **Female**	 6 75% 2 25%	 38 73.1% 14 26.9%	P=0.6
Age	8.7± 4.8	4.0± 2.6	P=0.0001
Fever	0	19 36.5%	
Hepatosplenomegaly	0	15 28.8%	
LN	2	17 32.7%	0.5
mucositis	2	19 36.5%	0.4
WBCs x $10^3/mm^3$	34.5± 24	42.2± 32.0	0.6
HB g/dl	7.7± 2.6	10.3 ± 1.4	P=0.0001
RBCsx10^6/l	3.9± 1.2	3.7± 0.8	P=0.4
Platelets x $10^3/mm^3$	40.5± 16.3	54.03± 41.6	P=0.4
Neutrophils x $10^3/mm^3$	2.8± 0.4	2.8± 0.4	P=0.8
Lymphocytes x $10^3/mm^3$	32.9± 24.00	3.1± 2.1	P=0.9
Type **BALL** **TALL**	 6 75% 2 25%	 26 50% 26 50%	P=0.2

Fig.1 The combined EBV infections with HHV6 and HHV7 among patients



HHV6 versus EBV P=0.001

HHV7 versus EBV P=0.2

In the current study, there was significant association between B-ALL and EBV (89.5%, P=0.0001) that reflects the tropism of EBV for B cells and may indicate the close association of EBV infection is with the occurrence of B-ALL as indicated by previous finding [13]. However, EBV may also target T lymphocytes and this was described previously [20]. There are cumulative evidences that EBV induces malignant transformation of T-lymphocytes leading to EBV associated Hemophagocytic Lymphohistiocytosis, chronic active EBV infection T- or NK-cell lymphoproliferative diseases and T-ALL[21]. In vitro study supported the role of EBV in etiology of TALL [22].

In the present study, EBV+ALL had the characteristic clinical signs and laboratory findings associated with EBV namely significant hepatosplenomegaly (47.4%, P=0.01), with significant increase of total leucocytes counts (mean± SD46.5± 38.5, P=0.04) and absolute lymphocytosis (mean± SD 38.8± 3,2, P=0.02). These clinical signs are described to be clues for EBV reactivation in lymphoid tissues [23]. The presence of clinical signs of EBV reactivation in children with ALL associated by EBV viremia as detected by real time PCR, denotes that molecular method is suitable for diagnosis of EBV in those patients. Similar result was reported in patients with nasopharyngeal carcinoma by Ambinder (2017)[24].

The use of real time PCR for detection of EBV DNA free in plasma was used in the present study as it was reported to yield good results as that used for mononuclear cells [24]. Molecular laboratory investigations suggest a role for viral load measurement in predicting various EBV-associated tumors such as lymphoproliferative disorder and Hodgkin's disease. The high viremia load may be associated with development and even in the prognosis of ALL [25].

The distinguished finding of the present study was the significant association between EBV and HHV6 among patients with ALL. Previous studies have proposed that more than one type of herpes viruses potentiate the pathological effects in infectious

mononucleosis as well as among other diseases such as chronic fatigue syndrome and post transplantation disorders[26,27]. However, this finding is contradictory with other reported by Morales-Sánchez *et al.*, 2014[28]. The difference may be due to the difference in the geographic locations and the difference in the number of the included patients.

In the present study, other herpes viruses than EBV were studied namely HHV6 and HHV7. HHV6 has been suggested to have a role in hematological malignancies, though it is a lytic virus. This is due to its capability of transforming DNA in vitro studies [29,30]. Even, the genome of HHV-6 has been shown to be integrated to peripheral blood mononuclear cell DNA and its DNA sequences were isolated from pathologic samples of Hodgkin's disease [31] and even from peripheral blood mononuclear cells from patients with ALL and with TALL [32].

In the present study, there were statistically significant higher prevalence of HHV6 and HHV7 among ALL (16.7%, 13.3% respectively) compared to healthy children (3.3% and 8.3% respectively, P=0.0001). These findings are contradictory to previous findings reporting lower prevalence of HHV6 and HHV7 among patients with ALL [28, 33]. The presence of high prevalence of HHV6 and HHV7 in the current study may indicate the role of different geographical regions in the epidemiology of the association of viral infections with development of certain diseases. Moreover, herpes viruses usually act as potentiating pathogenic factors for each other in infectious mononucleosis. Whether this mechanism also contributes to the pathogenesis of ALL or not, needs further extensive studies.

The supporting evidence from the present study that HHV6 and HHV7 may be involved in infectious mononucleosis disease that may be associated with pathogenesis of ALL, were the association of significant clinical signs associated with lymphoid system involvement such as hepatosplenomegaly with these viral infections.

The age distribution of EBV, HHV6 and HHV7 among children with ALL had no significant association with certain age. However, there was increase in the prevalence of EBV (36.8%), HHV6 (40%) and HHV7 (75%) in age above 4 years. Moreover, there was significant predominance of males among infected children. Similar results were reported from previous study from Burkina Faso with more prevalence of EBV and HHV6 in male patients below 5 years [34].

In conclusion, EBV, HHV6 and HHV7 viruses were present in high rates in ALL which suggest a role for these viruses in pathogenesis of ALL. Further studies are required to validate this hypothesis.

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