Original Article

Comparison of Influenza, Metapneumovirus (HMPV) and Respiratory Syncytial Virus (RSV) in Children with Leukemia, with and Without Respiratory Symptoms

Anahita Sanaei Dashti[1], Majid Asgharzadeh[2*], Mohammad Rahim Kadivar[1] and Fariba Shirvani[3]

1. *Professor Alborzi Clinical Microbiology Research Center, Namazi Hospital, Shiraz Medical University, Shiraz, Iran*
2. *Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran*
3. *Pediatric Infections Research Center, Research Institute for Children Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

*** Corresponding author**

Majid Asgharzadeh, MD
Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran
Email: asgharzadeh.pedia@gmail.com

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Abstract

Background: Acute leukemia is the most prevalent hematologic malignancy in children and infections are the most prevalent complication in this group. There are few studies on viral respiratory infections in children with leukemia. This article aimed to study the frequency of influenza, Respiratory Syncytial Virus (RSV) and Human Metapneumovirus (HMPV) respiratory infections in children with leukemia.

Methods: This is a cross-sectional study on 110 children with leukemia referred to Amir Hospital (Shiraz) from Aug 23th 2015 to Feb 20th 2016. Fifty-five children had respiratory symptoms (Case group) and fifty-five children had no respiratory symptoms (Control group). RT-PCR was done on respiratory secretions for influenza, RSV and HMPV in both groups. Data was analyzed by SPSS for Windows version 18. A p value<0.05 was considered significant.

Results: RT-PCR for influenza, RSV or HMPV was positive in 14 children in case group and 3 children in control group (p=0.004). The 2 groups were significantly different for having family members with respiratory symptoms (p=0.001), having a history of antiviral drugs usage (p=0.008), duration of the last admission (p<0.05), fever (p=0.001), duration of fever (p<0.05), and neutropenia (p=0.002).

Conclusion: Symptomatic viral respiratory infections are prevalent in children with leukemia. Attention must be paid to respiratory viruses in leukemic children, and if available, specimens should be tested for the presence of influenza viruses, RSV and metapneumovirus.

Keywords: Influenza, Children, Leukemia, Metapneumovirus, Respiratory Syncytial Viruses

Introduction

Leukemia accounts for one third of malignancies in children under 14. Nowadays, supportive strategies have increased the life expectancy among these children (1). Infections are the most common complication during treatment process and the main cause of death in children with leukemia (2). It was primarily believed that infections in childhood leukemia are mainly caused by bacteria and fungi. However, studies have shown that up to one third of febrile children with underlying malignancies are infected by viral pathogens and 18% are affected by Respiratory Syncytial Virus (RSV), influenza virus and human metapneumovirus (HMPV) (2-4). In a study by Benites *et al*, the prevalence of infection by respiratory viruses was assessed by Real-Time multiplex Polymerase Chain Reaction (RT-PCR) in patients<21 years old who underwent chemotherapy. RSV, influenza virus and HMPV were reported in 8.7, 3.9 and 2.9 % of patients, respectively (2).Viral pathogens are responsible for viral infections in 14% of febrile neutropenic patients (4).

This study investigated the presence of RSV, influenza virus and HMPV in nasopharyngeal secretions of children with acute leukemia with and without respiratory symptoms. Therefore, an attempt was made to show the role of important respiratory viruses in patients with respiratory symptoms.

Materials and Methods

This is a cross-sectional study on children with acute leukemia admitted to Amir Hospital, Shiraz, Iran, from Aug 23th 2015 to Feb 20th 2016. After being checked by the executor of research project, 55 children with upper and lower respiratory symptoms and signs (Cases) and 55 children without any respiratory manifestations (Controls) were enrolled. Inclusion criteria in case group were age <18 years, confirmed diagnosis of acute leukemia by pediatric hematologist, having at least one upper or lower respiratory tract sign/symptom [Coryza (Nasal discharge and congestion), sore throat, stridor, post nasal discharge, cough, sputum, respiratory distress (i.e. tachypnea, cyanosis, nasal flaring, subcostal-intercostal-suprasternal retraction, grunting), rale, rhonchi, wheeze, shortness of breath]. Exclusion criteria for case group were antiviral drugs consumption and unwillingness to participate in the study. Inclusion criteria for control group were age <18 years and confirmed diagnosis of acute leukemia by pediatric hematologist. Exclusion criteria for control group were absence of any upper or lower respiratory signs and symptoms and unwillingness to participate in the study. Cases and control patients were selected by convenience sampling. After obtaining informed consent from parents/guardians, study variables were recorded in a researcher-made questionnaire and nasopharyngeal samples were obtained from all participants. The procedure had no financial burden for the patients.

Before sampling, the specimen collector washed hands and wore gloves and mask. The patient's head was straightened and for children, another person helped to complete the procedure. Nasopharyngeal specimens were collected by a flexible calcium alginate swab with aluminum shaft which was inserted through the nostrils deep to posterior nasopharynx by a trained doctor. If the length of inserted swab was equivalent to half of the distance between the tips of the nose to ear, the swab tip might reach the posterior nasopharynx. If the swab could not go that deep, it was withdrawn and passed through another nostril. If still not successful, patient was excluded from the study.

The swab was gently rotated and sited in place for 5 to 10 seconds in order to dislodge the columnar epithelial cells (5). Specimens were placed in Virus Transport Media (VTM), and immediately stored at -70°*C* for PCR procedure for RSV, influenza virus and HMPV. Data were analyzed by SPSS for Windows version 18 by chi-square and Fisher exact test. $p<0.05$ was considered significant.

Results

A total of 110 children (66 males, 44 females) with acute leukemia were studied. Fifty-five patients (35 males, 20 females, mean age 6.9±4.5 years) had at least one upper or lower respiratory tract sign/symptom (Cases) and 55 (31 males, 24 females, mean age 7.2±5.1 years) were asymptomatic (Controls). The two groups didn't significantly differ with regard to age ($p=0.8$) and sex ($p=0.4$).

Different types of malignancies in RT-PCR positive and negative groups are shown in table 1. Overall, 14 cases (6 influenza virus, 5 RSV and 3 HMPV) and 3

controls (5.4%) had positive RT-PCR results (p=0.004) (Table 2). The two groups were also significantly different for having family members with respiratory symptoms (p=0.001), having a history of antiviral drugs usage (p=0.008), duration of the last admission (p<0.05), fever (p=0.001), duration of fever (p<0.05), and neutropenia (p=0.002) (Table 3).

The frequency of fever was significantly higher in RT-PCR positive patients compared to RT-PCR negative group (47.05 vs. 24.7%, p=0.001). Duration of respiratory symptoms was also significantly different in positive and negative RT-PCR groups (p=0.02); however, other variables such as duration of last admission, duration of fever and neutropenia, duration of time lapsed after last discharge and this admission, duration of leukemia and duration of neutropenia were not significantly different between RT-PCR positive and negative groups (p>0.05) (Table 3).

Discussion

Complicated and time-consuming techniques such as culture, contaminated tissue biopsy and serology have been used previously for detection of viruses but nowadays, molecular techniques such as RT-PCR play an important role in epidemiologic studies of respiratory viruses among children and adults with cancer, increasing the sensitivity of the diagnosis (6). Upper and lower respiratory viral infections depend on geographic region, season and exposure and are mainly caused by influenza A and B virus, parainfluenza virus, RSV, adenovirus, rhinovirus and HMPV (7). Infections play an important role in hematologic malignancies' morbidity and mortality (8). Bacterial and fungal infections were to be the

Table 1. Different types of malignancies in RT-PCR positive and negative groups

Type of malignancy	RT-PCR positive (n=17)	RT-PCR negative (n=93)	Total
ALL, n (%)	9(15.3)	50(84.7)	59 (53)
AML, n (%)	2(14.3)	12(85.7)	14 (13)
HL, n (%)	0	6(100)	6 (6)
NHL, n (%)	6(19.4)	25(80.6)	31 (28)

ALL, Acute lymphocytic leukemia; AML, Acute myeloid leukemia; HL, Hodgkin lymphoma; NHL, non- Hodgkin lymphoma

Table 2. Results of positive RT-PCR for influenza, HMPV and RSV in case and control groups of leukemic children with and without respiratory symptoms

	Case	Control	Total
Influenza	6 (75%)	2 (25%)	8
HMPV	5 (83.3%)	1 (16.7%)	6
RSV	3 (100%)	0	3
Total	14 (82.4%)	3 (17.6%)	21

Table 3. Comparison of quantitative variables in case and control, RT-PCR positive and negative groups

	Case group (Mean±SD)	Control group (Mean±SD)	p value	RT-PCR +group (Mean±SD)	RT-PCR - group (Mean±SD)	p value
Duration of respiratory symptoms (Days)	5.03±1.9			4±2.5	2.2±2.8	0.02
Last admission duration (Days)	11.6±9.9	5.3±3.3	0.001	9±8.3	8.8±8.4	0.9
Time between previous discharge and admission (Days)	57.8±95.2	45.8±63.6	0.5	87.6±118.2	45.5±72.6	0.08
Duration of malignancy (Months)	13.9±14.1	15.4±18.4	0.6	20.9±27.5	13.5±13.3	0.08
Duration of fever (Days)	1.9±2.9	4±1.5	0.001	1.8±2.4	1.05±2.4	0.2
Duration of neutropenia (Days)	2.3±4.5	1.1±2.8	0.08	1.6±2.9	1.7±4	0.9

main pathogens in patients with malignancies but with improvements in diagnostic techniques, the role of viral infections in the mortality and morbidity of these patients has become more prominent (9,10).

About 43.5% of infections in children with ALL are respiratory infections and 88.5% of them are upper respiratory tract infections (11). In our study, RT-PCR results were positive in 17 patients, 14 belonging to case group (6 influenza virus, 5 RSV and 3 HMPV). In other studies on neutropenic children with hematologic malignancies, viral respiratory infection was detected in 14% of febrile neutropenic children (4) and RSV, influenza A, B virus and HMPV were respectively detected in 8.7, 3.9 and 2.9% of children with viral infections under chemotherapy (2). In a study on children with leukemia, in 138 cases with fever, 61 of 138 febrile patients were infected with respiratory viruses, 12 types of respiratory viruses were isolated and most commonly isolated viruses were rhinovirus (22%), RSV (11%), human bocavirus (5%) and influenza virus (4%). Mean fever duration was 2.6 days in virus positive and 2.1 in virus negative cases (12). In our study, duration of fever was significantly higher in children with respiratory infections ($p<0.05$). The presence of neutropenia was significantly higher in children with respiratory infections ($p=0.002$). In a prospective study on febrile neutropenic children, viral infection was detected in 44% of cases and rhinovirus (22%) and RSV (11%) were the most common viruses (13). Viral respiratory infections often have coinfection with fungal and bacterial infections. This finding was shown in a study on children with oncologic problems among which 39% had RSV infection (14). One of the most important complications of viral infections is the need to postpone chemotherapy in children with respiratory infections. Almost 50% of oncologic patients have approximately 7 days of treatment delay because of viral infections (15).

Limitation of this study was low number of cases in each group and its advantage was preforming viral test with an accurate and standard instrument, and low probability of inter- and intra- observer bias.

Conclusion

Based on the results of this study, physicians should be aware of respiratory infections in hematology and oncology patients, especially in the case of fever and respiratory signs and symptoms. Antiviral drugs play an important role in their treatment strategy. RT- PCR technique provides a higher rate of detection of these organisms and can help in diagnosis and treatment plan of these patients.

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