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Respiratory Viral Infectious Aetiologies of Transient Cytopenia in Previously Healthy Children

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Abstract

Background and Aims: Transient cytopenia due to infectious agents is frequent in childhood. Clinical picture changes between mild to life-threatening conditions. In this study, viral aetiology of previously healthy children admitted with viral symptoms and cytopenia were evaluated. ***Methods:*** Children admitted from January to April 2015 were included. Children with chronic diseases and previous neutropenia were excluded. Their demographic features and aetiological viral pathogens were evaluated retrospectively. ***Results:*** Twenty-nine patients (17 male [58.6%], 12 female [41.4%]), whose mean age was 63.3±38.9 months, were included. Symptoms started median 5 (2-10) days before the admission. Admission symptoms were as follows; nasal symptom (n=27, 93%), cough (n=27, 93%), fever (n=25, 86.2%), GIS symptoms (vomiting, diarrhoea, and abdominal pain) (n=20, 69%), arthralgia (n=12, 41%), myalgia (n=11, 37.9%), skin eruption (n=7, 24.1%), and respiratory distress (n=4, 13.8%). Twenty-two patients (75,8%) had leukopenia, 19 (61.3%) children had neutropenia, 3 (9.6%) had thrombocytopenia, and 9 (29%) had leukopenia, neutropenia and thrombocytopenia. Respiratory viral Polymerase Chain Reaction was positive in 21 (67.7%) children. The distribution of viruses was as follows; influenza A, 11 (H1N1, 8; H3N2, 3); influenza B, 5; rhinovirus, 3; respiratory syncytial virus, 2. None of the children had more than one virus. Cytopenia was shown to resolve median 12 days (7-28) after the onset of symptoms. ***Conclusion:*** Viral pathogens accompanying cytopenia are various. The recovery from cytopenia is rapid.

Key words Acquired; Children; Cytopenia; Healthy; Transient

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Introduction

Acquired cytopenia in childhood is common in paediatric practice.[1] The differential diagnoses range from severe life-threatening disease to transient, self-limited, benign conditions of little clinical importance.[2,3] Transient infectious cytopenia is one of the most frequent reasons of acquired cytopenia, with mild to moderate severity and spontaneous recovery within several days or weeks.[4,5] On the other hand, it is considerably important to differentiate it from severe conditions, such as primary immunodeficiencies, systemic autoimmune diseases, congenital bone marrow failure syndromes, or malignancies.

Various viruses, mostly Epstein-Barr virus, cytomegalovirus, parvovirus B19, human immunodeficiency virus, and nairovirus present with haematological manifestations

including anaemia, neutropenia, thrombocytopenia and pancytopenia[6,7] and haematological results of viral infections usually appear in the early phase of acute infections.[6]

There is a limited data in the literature on haematological consequences of respiratory virus infections. Haematological effects of H1N1 virus especially during the pandemia in 2009 were reported.[6,8] Herein, we report haematological manifestations of respiratory viral infections in previously healthy children with febrile illness.

Methods

A total of 29 previously healthy Caucasian children who were admitted due to febrile cytopenia and flu symptoms between January 2015 and April 2015 were enrolled in the study. In all children, the initial evaluation was based on a detailed history regarding presence of any previous medical treatment or underlying disease and a thorough clinical examination. Data collected from each medical record included age, sex, type and length of symptoms, physical examination findings, and length of neutropenia duration. Patients with other primary diagnoses known to cause any kind of cytopenia or patients who were under medication that could lead to neutropenia or chronic neutropenia were excluded from the study.

Initial laboratory work-up comprised complete blood count with differential, peripheral blood smear, C-reactive protein, erythrocyte sedimentation rate, cultures of blood and urine, serological tests for infectious agents (serum antibody levels of Epstein-Barr virus, cytomegalovirus, and parvovirus), and nasopharyngeal swap for respiratory viruses.

Nasopharyngeal and throat swabs collected from patients were sent to the laboratory in virus transport medium (Virocult). RNA extraction was performed using Qiagen EZ1Virus Mini Kit v2.0 (Qiagen, Germany) according to manufacturer's instructions. Then multiplex Real-Time Polymerase Chain Reaction (PCR) test was performed with Fast Track Diagnostics/Respiratory Pathogens 21 (Luxemburg) kit detecting respiratory pathogens including influenza virus A, B, A/H1N1, human respiratory syncytial virus, human parainfluenza virus type 1,2,3,4; human bocavirus, enterovirus, rhinovirus, parechovirus, human metapneumovirus, human coronaviruses, and adenovirus.

Leukopenia was defined as a white blood cell count of <4500/μL, while neutropenia was defined as an absolute neutrophil count (ANC) of <1500/μL for children aged more than 12 months and <1000/μL in younger ones.[9,10] The severity of neutropenia was characterised as mild (ANC of 1001-1500/μL), moderate (ANC of 500-1000/μL), or severe (ANC less than 500/μL).[11] Thrombocytopenia was grouped as mild (platelet count: 50.001-150.000/μL), moderate (20.000-50.000/μL), and severe (<20.000/μL). Transient cytopenia was defined as cytopenia lasting for less than 6 months.

Data analysis was performed using the Statistical package for the Social Sciences version 18.0 (Chicago, IL, USA). Categorical variables were compared using a chi-square test, while the Fischers' exact test was used to compare the percentages between small groups of patients. Comparisons between groups were performed using the Kruskal_Wallis one-way analysis of varience (ANOVA), and *t*-test. Pearson and spearman correlations were used for the association of cytopenia duration with its severity. Statistical significance was set as at 0.05.

Results

The mean age of the group was 63.3±38.9 months (2-144 months) and 17 (58.6%) of the patients were male. Most of the patients (62.1%) were younger than 5-year of age. Infectious symptoms started median 5 (2-10) days before the admission. Admission symptoms were as follows; nasal symptom (n=27, 93%), cough (n=27, 93%), fever (n=25, 86.2%), GIS symptoms (vomiting, diarrhoea, and abdominal pain) (n=20, 69%), arthralgia (n=12, 41%), myalgia (n=11, 37.9%), skin eruption (n=7, 24.1%), and respiratory distress (n=4, 13.8%).

The results of cultures and acute phase reactants discarded presence of any primary or secondary bacterial infections. Haematological findings of the patients are summarised in Table 1. Twenty-two patients (75.8%) had leukopenia, 19 (61.3%) had neutropenia, 3 (9.6%) had thrombocytopenia, and 7 (24.1%) had leukopenia + neutropenia + thrombocytopenia. Neutropenia was observed in 4 patients

Table 1 Haematological findings of the patients*

WBC (x10^3/μL)	3.3 (1.7-11)
ANC (x10^3/μL)	0.7 (0.1-38)
Haemoglobin (g/dl)	12.9 (11.3-15.4)
Thrombocyte count (x10^3/μL)	173 (45-509)

*median (minimum-maximum)

WBC; white blood cell count, ANC; absolute neutrophil count

without leukopenia. Of 26 neutropenic patients, 21 (80.8%) patients had neutrophil count below 1000/μL and 5 (19.2%) had below 500/μL. Median leukocyte count of leukopenic patients was 2840/μL (min-max: 1700-4280), median neutrophil count of neutropenic patients was 760/μL (min-max: 130-990), while median thrombocyte count of thrombocytopenic patients was 97.000/μL (min-max: 45.900-142.000). None of the patients had anaemia related to haemolysis or iron deficiency and no direct relation between anaemia and respiratory viral agents could be established.

Respiratory viral PCR analysis was positive in 21 (67.7%) children and mostly isolated viral agent was influenza A (n=11, 52.3% [H1N1, 8; H3N2, 3]). The distribution of viruses was shown in Table 2. None of the children had more than one virus. Serological investigation of Epstein-Barr virus, cytomegalovirus, and parvovirus was not compatible with active infection.

Cytopenia was shown to resolve median 12 days (min-max: 7-28) after the onset of symptoms. Of 29 patients, recovery from cytopenia seen in 4 (13.8%) patients in the first week, 15 (51.7%) patients in the second week, 6 (20.7%) patients in the third week, and 4 (13.8%) patients in the fourth week. All of the patients had normal levels of blood cells at the end of 28 days after the onset of viral symptoms. None of the patients had cytopenia longer than 4 weeks, and thus none needed further evaluation, for example, bone marrow examination. When 3 subgroups of patients with mild, moderate and severe neutropenia were compared, no significant correlation was present regarding the severity of neutropenia and duration of recovery of neutropenia. Also there was no association between the viral pathogens and the duration of neutropenia.

Discussion

This study has shown that regardless of the virus type, reduction in any series of blood cells could be seen in the course of respiratory viral infections in otherwise healthy children. Cytopenias due to viruses may take place by several mechanisms, such as decreased production, in which concomitant use of drugs may have an additive effect, viral suppression of bone marrow, inhibitory effects of the inflammatory cytokines, bone marrow necrosis or increased loss including haemolysis, haemophagocytosis, or immune thrombocytopenic purpura.[6] Previous studies have been conducted to exhibit clinical course, management, and aetiology of febrile cytopenia in previously healthy children.[3,9,11] Nevertheless, there is limited data in the literature regarding haematological consequences of respiratory viral infections.

Table 2 The distribution of respiratory viruses

Identified respiratory viruses	n (%)
Influenza A	
H1N1	8 (38.1)
H3N	3 (14.3)
Influenza B	5 (23.8)
Rhinovirus	3 (14.3)
Respiratory syncytial virus	2 (9.5)

In the present study, neutropenia (61.3%) was the commonest type of cytopenia. Also in 24.1% of the patients it was accompanying thrombocytopenia. In previous studies, Karavanaki et al,[9] Vlacha & Feketea,[3] and Kagialis-Girard[12] et al reported bilineage cytopenia associated with infectious cytopenia, of which anaemia had been the most common finding associated with neutropenia. In contrast, an association was not found between anaemia and viruses as there was no anaemic patient in our study. It was reported in several studies that post-infectious transient neutropenia has been predominantly mild or moderate in severity.[1,13-15] Mild neutropenia was not observed in our study. It is known that febrile neutropenia in patients with malignancy or on chemotherapy or other immunosuppressive drugs possess high degree of morbidity and mortality. Despite all of the patients had moderate or severe neutropenia, any serious infection has not been experienced in the study patients.

Cytopenia was shown to resolve median 12 days after the onset of symptoms in our study. This is significantly shorter duration for recovery when compared with malignancy or chemotherapy induced cytopenias. Among all the study patients recovery of cytopenia was mostly (65.5%) seen within two weeks. Alexandropoulou et al[1] reported that respiratory syncytial virus (RSV) had an association with prolonged neutropenia (>30 days). On the contrary, in this study, at the end of 28th days, it was realised that all of the patients had normal levels of blood cells. The studies by Serwint et al[16] and Vlacha & Feketea[3] reported similar results, which ranged between 3 to 23 days.

Respiratory viral PCR analysis was positive in 21 (67.7%) children and mostly isolated viral agent was influenza A (n=11, 52.3% [H1N1, 8; H3N2, 3]) in this study. Complications associated with influenza viruses bear on mostly upper and lower respiratory tract, nervous system,

and cardiac involvement. Their effects on haematological system have been reported as leukopenia, lymphopenia, moderate thrombocytopenia for especially clinically moderate to severe patients.[17] As well as influenza viruses, especially lymphopenia in association with RSV bronchiolitis was reported and it was demonstrated that an inverse correlation between lymphocyte count and severity of illness was present.[18] Cytopenia associated with rhinovirus is not a frequent condition, related to its localised and mild inflammatory response. Nevertheless, interestingly, this virus was isolated in 3 patients in present study.

The ages of the patients in our study were consistent with other reports, which may confirm that transient cytopenia is mostly observed in young infants and children.[3,9,13,19] The effect of young age on infection related neutropenia could be attributed to an age related susceptibility to myeloid insult.[2] Nevertheless, no difference was found between monocytopenia or bicytopenia and the ages of the patients. Also, our study revealed that most of our patients were boys (58.6%). A gender differentiation was observed in transient cytopenia with male predominance and this finding has been supported by similar results of previous studies.[3,9,16,20]

Conclusion

In conclusion, it is obvious that cytopenia during viral febrile illnesses is common among previously healthy children and viruses may affect one or more cell lines. This study showed that regardless of the type of respiratory viral agent, the causal infectious cytopenias were self-limited and resolved within one month.

Declaration of Interest

The authors declare that there is no conflict of interest.

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