RESEARCH ARTICLE

Systemic Inflammatory Response and Chronic Herpesvirus Infections in Children

Fatkullina Guzel Roaldovna[1], Ustinov Arthur Eduardovich[2], Afonin Pavel Andreevich[3]

[1]Department of Children's Infections, Kazan State Medical University, Kazan, Butlerova St., 49, Russia, [2]Department of the General Management, Institute of Management, Economics and Finance, Kazan Federal University, Kazan, Kremlevskaya St., 18, Russia, [3]Student 4 Courses, Kazan Federal University Higher Institute for Information Technology and Information Systems, Kazan Federal University, Kazan, Kremlevskaya St., 18, Russia

Abstract

Aim and Scope: This paper presents the material and results of clinical studies of herpesvirus infections, posing currently an urgent problem for both healthcare and society as a whole. Today, the state of chronic inflammation, responsible for the development of a number of pathological processes in human, attracts a great interest of researchers. Along with this, it is also worthwhile to pay attention to the indicator such as burden of the disease. **Materials and Methods:** Due to the severity of the disease and its long treatment period, it seems important to effectively treat patients with the task of reducing the burden of the disease. In terms of the economic burden, the proposed approach is less expensive. For parents, the burden of the disease on the proposed approach is less by 4.98 times compared with the traditional approach. For the state, the burden on the proposed approach is less by 5.71 times compared with the traditional approach. According to the proposed method, the period of full recovery was 2 months. Traditional method, at the same time, ensured only temporary improvement. **Result and Discussion:** The examined patients sought medical help with a large number of complaints and symptoms. Attention was paid to a decrease in the hemoglobin level in some patients. The majority of patients (71.7%) had degree 1 anemia; the second degree was diagnosed in 18.5% of children, and the third in 10.3% of the examined patients. Later, to verify the type of anemia, a comprehensive evaluation of the ferrokinetic indicators was carried out. **Conclusion:** The disease lasted for 1.5 years (18 months) until the proposed approach was applied.

Key words: Cytomegalovirus, disease burden, Epstein–Barr virus, Herpesvirus infections, human herpesvirus 6, quality of life, sickly children

INTRODUCTION

Herpesviral infections (HVI) are today an urgent health problem, due to their ubiquitousness, the ability to cause various forms of the pathological process in the human body and affect all organs and systems.[1] According to the WHO definition, we are currently experiencing a pandemic of herpesvirus infections, as evidenced by the vast number of both adults and children infected with different strains of viruses of the *Herpesviridae* family, reaching 65–90%.[2-8]

Today, the state of chronic inflammation, responsible for the development of a number of pathological processes in humans, such as endothelial dysfunction, atherosclerosis, immune dysfunction in infectious diseases, and anemia of a chronic disease, attracts a great interest of researchers.[9-14] Chronic inflammatory reaction (CIR) is formed against the background of persistent hyperactivation of the immune system (excessive production of pro-inflammatory cytokines). Changes in the cytokine profile system, i.e., hyperproduction of pro-inflammatory cytokines, are associated with the formation and progression of a number of severe pathological conditions associated with chronic HVIs.[15-20]

The prevalence of anemia is considered an indicative measure of the nation's health, traditionally evaluated by

Address for correspondence:
Fatkullina Guzel Roaldovna, Department of Children's Infections, Kazan State Medical University, Kazan, Butlerova St., 49, Russia.
E-mail: Ftkguzel@mail.ru

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public health authorities.[21] Worldwide, the most common cause of anemia is iron deficiency in the body. Along with this, its development is traditionally associated with other causes, which among others traditionally include vitamin deficiency, prolonged inflammatory processes, defects in the formation of red blood cells, congenital, or acquired disorders in hemoglobin synthesis processes.[21] The nature of anemia itself is associated with a number of chronic diseases.[21,22]

The main factor of the pathogenesis of anemia of chronic disease (ACD), a component of the systemic inflammatory response, is a long-lasting excess level of pro-inflammatory cytokines in tissues (chronic inflammation!), leading to a redistribution of iron and disruption of subsequent mechanisms for its reutilization.[23,24] Chronic diseases associated with ACD are accompanied by activation of the macrophage system, which firmly "holds" iron and thus impairs the process of its utilization by hematopoietic cells. Complete blood count of such patients shows a moderate decrease in hemoglobin level against a background of normal or even excessive accumulation of iron in tissues.[24,25]

In practical terms, determining the type of anemia is certainly an important step, since the unreasonable prescription of iron drugs (which is often observed in practice) is not only useless but also harmful in a certain sense, since it leads to dystrophy of the gastrointestinal mucosa, hemosiderosis, and generalized bacterial processes.[24-26]

Among the possible "culprits" for the development of ACD, various variants of HVI can be classified.[24]

The objective of the research was to determine the prevalence of markers of systemic inflammation in patients with chronic HVI caused by human herpesvirus type 6 (HHV 6), Epstein–Barr virus (EBV), cytomegalovirus (CMV), and mixed HVIs and to determine the cost of treatment with the identification of an economic disease burden for the patient and the state.

METHODS

A group of 154 children with various nosological forms of herpetic infections was examined: HHV-6 infection - 41, EBVI - 37, CMVI - 32, and mixed HVIs - 44 patients. The age of those surveyed is from 1.5 to 15 years (boys - 89 and girls - 65). The patients were managed both on outpatient and inpatient basis in the infectious hospital (Kazan DCIH).

Study entry criteria: The presence of clinical symptoms of a chronic infectious process. The mandatory requirement for inclusion in the group was the markers of the activity of one or more studied viral infections, the presence of two or more of the listed clinical symptoms - fever, lymphadenopathy, exanthema, recurrent episodes of acute respiratory disease, hepatosplenomegaly, and gastrointestinal dysfunction on the background of torpid IDB lasting over 3 months, and repeated episodes of lowering hemoglobin levels. As an anemia criterion, according to the WHO recommendations,[1] Hb values below 110 g/l were considered for children aged 6 months to 5 years; below 115 g/l for children aged 5–11 years, and below 120 g/l for children over 12 years old.

To verify the diagnosis of HVI, an enzyme immunoassay was used to determine the presence of antibodies to CMV antigens - IgG and G; an estimate of the avidity index - IgG to antigens of the HHV-6, IgM to the capsid antigen, IgG to the early, and nuclear antigens of the EBV in the blood serum; and polymerase chain reaction with the determination of DNA of the HHV-6, EBV, and CMV in the blood serum and DNA of the HHV-6 in saliva. The following ferrokinetic parameters were evaluated: Erythrocyte indices - mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) and metabolic parameters of iron: Serum iron, total iron-binding capacity of serum (TIBC), ferritin, and iron transferrin saturation coefficient (TSC). The markers of the systemic inflammatory response (SIR) and markers of inflammation were identified: C-reactive protein, serum aspartate aminotransferase (AST), erythrocyte sedimentation rate (ESR), tumor necrosis factor-a (TNFa), creatine phosphokinase (CPK), cardiac subunit of creatine phosphokinase (CK-MB), and myoglobin.

Resolution 58.33 of the World Health Assembly 2005, signed by the Russian Federation, declares the pursuance of full accessibility of health services for every person. The likelihood of achieving better results increases with more efficient use of existing resources. The basic is the calculation of the cost of a specific disease for one patient.

The total cost of the disease will be the sum of all the stages of therapy included in the analysis:

Cost = Diagnosis + Outpatient stage + Inpatient stage + Rehabilitation.

The analysis of the cost of illness is a descriptive analysis of the cost of managing patients suffering from a disease and is based on epidemiological data. This method allows for the absence of an alternative; its methodology consists in simply adding up all used costs.

According to the analysis of economic indicators, the materials from pharmaceutical networks and data from the State Statistics Committee of the Russian Federation were used.

The scheme and composition of the given medical prescriptions are taken from the existing practice of treating the presented diseases.

RESULTS

The examined patients sought medical help with a large number of complaints and symptoms. The most

common were as follows: Prolonged fever, persistent lymphadenopathy, frequent upper respiratory tract disease, weakness, polymorphic exanthema with a long "flowering" period, frequent dysfunction of the gastrointestinal tract, and lymphomonocytosis in the peripheral blood [Figure 1]. This symptomatology characterizes, according to the literature, chronic herpesvirus infections.[4,24,27,28]

Chronic mononucleosis (117)
Chronic active herpesvirus infection with CNS involvement (19)
Chronic hepatitis (7)
Viral pneumonitis (5)
Mononucleosis-free cutaneous disease (4)
Chronic fatigue syndrome (2)

Attention was drawn by a decrease in the hemoglobin level in some patients, quite rigid to earlier attempts to treat it with iron drugs. The frequency of anemia was quite high and was registered in every fourth child (25% - 39 patients). The timing median of anemia since the onset of symptoms of an infectious disease was 6 and ½ months.

The majority of patients (71.7%) had degree 1 anemia; the second degree was diagnosed in 18.5% of children, and the third in 10.3% of the examined patients. Later, to verify the type of anemia, a comprehensive evaluation of the ferrokinetic indicators was carried out [Table 1].

Table 1: Ferrokinetic indicators in children with chronic HVI (*n*=39)

MCV (70–100 fl)	17 (43.6)	22 (56.4)	0 (0)
MCH (24–33 pg)	14 (35.9)	25 (64.1)	0 (0)
IS (8.9–21.5 μmol/l)	15 (38.5)	24 (61.5)	0 (0)
TIBC (40.6–62.5 μmol/l)	11 (28.2)	23 (58.9)	5 (12.8)
TSC (15–45%)	31 (79.5)	8 (20,5)	0 (0)
Ferritin (30–140 ng/ml)	6 (15.4)	20 (51.3)	13 (33.3)

HVI: Herpesviral infections, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, TIBC: Total iron-binding capacity of serum, TSC: Transferrin saturation coefficient

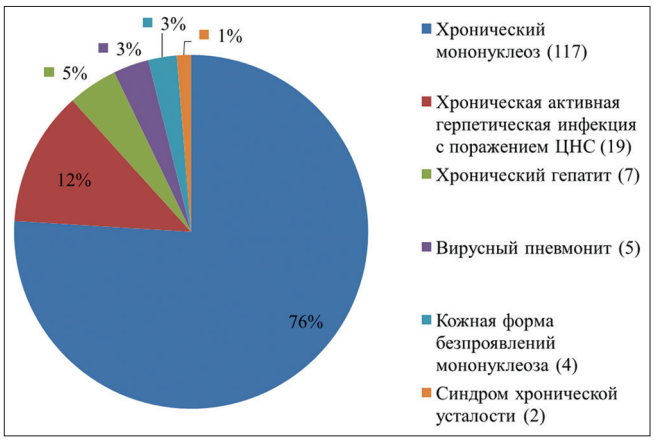

Figure 1: Clinical variants of herpetic infection in the examined patients (*n* = 154)

DISCUSSION

The primary information on the possible cause of anemia can be obtained already in the analysis of erythrocyte indices: MCV and MCH. It is known that iron-deficiency anemia (IDA) is characterized by a significant decrease in MCV and MCH.[24] As can be seen from the table, erythrocyte indices in most patients (56.4% and 64.1%, respectively) did not differ from the conventionally normal ones. According to the data given in Table 1, it can be seen that the parameters of IS and TIBC in most patients (61.5% and 58.9%, respectively) were in the normal range, which indicates a sufficient amount of iron in the body. Another important factor that allows differentiating the true and redistributive iron deficiency is the serum ferritin level. As is known, in ACD, this indicator rises to any extent. In our study, in 84.6% of patients, ferritin was determined within the age limit or even exceeded the conventional normal parameters, which indicates a sufficient content of iron in the depot.[24,29] The fact that the level of TIBC was below the normal or within its limits in 28.2% and 58.9%, respectively, also counts in favor of ACD. Otherwise, in IDA, as is known, this parameter grows.[23-25]

Our observations showed that ACD occupies a significant place (33.3%) in the structure of anemia in the observed patients.[24] Since iron is present in sufficient quantities in the patients with ACD, the prescription of iron drugs is useless and poses a danger of possible development of various complications.[24,26,30] A pathogenetically justified effect on the root cause of this phenomenon is a chronic inflammatory process.[24] In our case, it is a herpesvirus infection in various forms.

Patients with ACD and IDA (19 children in total) received antiviral therapy (without the use of iron preparations). The study involved patients with microspherocytic hypochromic anemia, with TSC <15%. In this case, patients with IDA were treated with children with a ferritin level of <30 ng/ml.

Twelve of 13 patients with ACD had their hemoglobin level reaching normal values after antiviral therapy. In IDA, the effect without prescribing treatment was recorded in only one patient (perhaps, this patient had mixed anemia). No effect was observed of the therapy of the underlying disease and in one patient with ACD.

The majority of patients suffering from anemia in chronic HVI during the antiviral therapy achieved a positive effect for a number of ferrokinetic indicators. All this once again confirmed the opinion about the prevalence of ACD in the range of causes of anemia.[24]

Along with the ferrokinetic parameters, an analysis of other SIR markers was carried out. The results are shown in Figure 2.

As can be seen in Figure 2, as a result of a combination, serial antiviral therapy, 100% of patients achieved the following

SIR markers: CK-MB; myoglobin; and TNFa. As for other SIR parameters, the best progress was noted in terms of the level of CPK - after therapy, it remained high only in 0.6% of the subjects. ESR and AST achieved normal values as a result of the therapeutic measures in 79.5% and 67.6% of patients, respectively.

The analysis of the economic effect included analysis of the traditional and proposed approaches. The maximum incidence among children is observed at the age of 6 months to 6 years and ranges from 4 to 6 times per year. This pattern can be traced in children in all countries of the world, regardless of the economic level of their development (in the Russian Federation on the basis of the statistic data of the Ministry of Health of the Russian Federation).

The national pediatrics usually classifies children as sickly based on their age and the criteria proposed by A.A. Baranov and V.Iu. Albitskii in 1986 [Table 2].

It was also noted that sickly children are more prone to the development of neurotic reactions; they become tired more quickly, study worse. This situation is potentially dangerous from the point of view of the formation of pedagogical problems (low achievement, lagging behind the curriculum, etc.). In addition, the psychological climate in the family suffers. Thus, it has been established that recurrent respiratory diseases in children in more than 50% of families are accompanied by moderately or significantly strained relations between parents and more than 57% - a lack of attention to other family members, including other children. In general, it is shown that more than 70% of parents, whose children are often ill with acute respiratory distress, note a deterioration in their quality of life.[31]

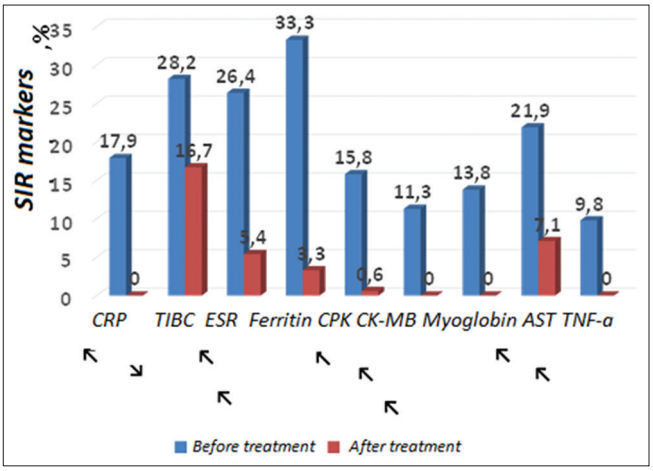

Figure 2: Systemic inflammatory response markers in patients with herpesviral infections (n=154), %

Table 2: A group of sickly children

Age	Number of ARD episodes per year
0–1 year	4 or more
1–3 years	6 or more
4–5 years	5 or more
Over 5 years	4 or more

Let us calculate the disease burden in the traditional approach of diagnosis and treatment and in the proposed variant.

Initial data for calculation and analysis:

1. A 5-year-old child.
2. There is a caregiver.
3. This caregiver works. The average salary, the contribution to the state GDP - according to Rosstat.
4. The cost of therapy is determined in accordance with the cost of medication.
5. GDP per 1 working person is about 464.52 thousand rubles or 38.71 thousand rubles per month.
6. Number of relapses * number of hospital days = total number of days of illness (5*10=50 days or 1.67 months.)
7. Direct losses to GDP per year per a caregiver are 90,668.475 rubles (the current situation). 38.71 thousand rubles per months*10 (days of inpatient stay)/30 (number of days of months) = 12,903.33 rubles.
8. 210 rubles - the cost of complete blood count test.
9. 190 rubles - HHV-6 test.

The average salary in the Russian Federation is 36,195 rubles.

The amount of payment as per the fit note is 18,097.5 rubles.

For this purpose, we further note that the burden of the disease should be considered from various angles and the burden of the disease for the state and the burden of the disease for the patient are of a different socioeconomic nature [Tables 3-5].

SUMMARY

The ratio of efficiency and cost of treatment by the traditional and proposed method:

In terms of the economic burden, the proposed approach is less expensive. For parents, the burden of the disease on the proposed approach is less by 4.98 times compared with the traditional approach. For the state, the burden on the proposed approach is less by 5.71 times compared with the traditional approach.

According to the proposed method, the period of full recovery was 2 months. Traditional method, at the same time, ensured only temporary improvement. The disease lasted for 1.5 years (18 months) until the proposed approach was applied. Thus, it is possible to estimate the increase in the effectiveness of the new approach as by approximately 9 times in terms of the recovery period.

Table 3: The list and total cost of medicines and procedures in the traditional treatment

Medicine/procedure	Unit cost, rub.	Amount (a package, ml, l, a procedure)	Total cost, rub.
Hemomycin	220.28	3	660.84
Genferon light 125 thousand units	288	6	1728
Berodual	284	3	852
Singulair	1100	1	1100
Nasonex	490	3	1470
Zyrtec	237	1	237
Aktiferrin	191	2	382
Maltofer	877	2	1754
Glucose 5% 500 ml	128	5	640
Albumin 100 ml	1692	5	8460
Acesol 400 ml	34	5	170
Chlosol 400 ml	43	5	215
Trisol 400 ml	38	5	190
RBC transfusion	1000	3	3000
Plasma transfusion	1000	3	3000
Total cost, rub.			23,858.84

RBC: Red blood cell

Table 4: The disease burden for the state

Item	Traditional approach	Proposed approach
Cost of primary examination	260	260
Cost of inpatient treatment (10 days)	16800	16800
Number of relapses per year	5 per year. 2×inpatient treatment	-
Cost of medication		
Treatment of severe disease	20,439.65*(2/5)=8,175.86	600
Treatment of underlying disease	-	600
Impact on gross domestic product	101,344	10,557
Health improvement of sickly children	20,000	-
Total	260*5+16,800*2+8,175.86+101,344+20,000=164,419.86	28,817
Disease burden	5.71 times higher	

Table 5: The burden of the disease for parents (child care)

Item	Traditional approach	Proposed approach
Cost of primary examination	260	260+190 HHV-6 test
Cost of inpatient treatment (10 days)	16,800	16,800
Number of relapses per year	5 per year. 2×inpatient treatment	0
Cost of medication		
Treatment of severe disease	23,858.84*(2/5)=9,543.54	600
Treatment of underlying disease	-	600
Impact on gross domestic product	90,668.475	12,903.33333
Health improvement of sickly children	20,000	0
Total	260*5+16,800*2+9,543.54+90,668.475+20,000+210*5=156,162.015	31,353.33
Disease burden	4.98 times higher	4.98

CONCLUSIONS

- The wide prevalence of ACD among patients with chronic forms of HVI speaks in favor of the development of a CIR, which undoubtedly proves the need for a comprehensive evaluation of the ferrokinetic parameters followed by therapy for the underlying disease.
- This kind of tactics is undoubtedly not universal, but taking into account the prevalence of ACD, such medical behavior seems justified to us. Further diagnostic activity will require a comprehensive assessment of ferrokinetic indicators and a final decision on the prescription of iron drugs.
- The identification of a set of SIR markers is a convenient tool in terms of developing diagnostic, and subsequently, therapeutic algorithms available to clinical institutions.
- The results obtained allow avoiding the prescription of inappropriate drugs and thus reduced the risk of complications and adverse events.

- An economic effect can be considered additional, which manifests itself in reducing the burden of the disease directly for the patient (in the case of children), parents, and the state.

In connection with the reduced time and cost of treatment and the achievement of the stage of full recovery, it is worthwhile to note the improvement in the quality of life of the patients and their families.

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