CATAMNESIS OF CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION DEPENDING ON ETIOTROPIC THERAPY IN THE FIRST YEAR OF LIFE

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Cytomegalovirus infection (CMVI) continues to be a serious public health problem, being second to hypoxia and asphyxia in the list of reasons of morbidity and mortality of newborns. This study aimed to analyze therapeutic approaches to management of children with congenital cytomegalovirus with the regimens including an antiviral drug (direct action) and a specific anti-cytomegalovirus immunoglobulin (anti-CMV IG), depending on the clinical form of the disease. The total number of participants was 62, with the first group of children receiving the antiviral drug (n = 21), and the second group — an anti-CMV IG (n = 41). We analyzed the clinical, laboratory and instrumental research methods, and studied the catamnesis of children under 3 years of age. For statistical analysis, we used SPSS Statistics and StatTech v.3.1.6. In the first group, where the regimen included the direct action antiviral drug, the outcome was successful for 28.6% of the participants, and in the second group, which was treated with the anti-CMV immunoglobulin, this figure was 58.5%. Regardless of the regimen, by the age of 3, 50% of the children were practically healthy. Most of the participants tolerated the therapy satisfactorily. However, for 66% of the involved children, we had to shorten the direct action antiviral drug therapy to 14 days because of the problems with venous access, in 4.8% we registered thrombocytopenia, and in 9.5% — increased transaminase activity. Comparing the disease outcomes depending on the therapy initiation day, we established significant differences only for the specific antiviral therapy cases (p = 0.044).

Keywords: congenital cytomegalovirus infection, gancyclovir, anti-CMV immunoglobulin, outcomes

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КАТАМНЕЗ ДЕТЕЙ С ВРОЖДЕННОЙ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИЕЙ В ЗАВИСИМОСТИ ОТ ЭТИОТРОПНОЙ ТЕРАПИИ НА ПЕРВОМ ГОДУ ЖИЗНИ

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Цитомегаловирусная инфекция (ЦМВИ) продолжает оставаться серьезной проблемой общественного здравоохранения, занимая второе место после гипоксии и асфиксии в структуре заболеваемости и смертности новорожденных. Целью исследования было проанализировать лечебные подходы к ведению детей с врожденной цитомегаловирусной инфекцией с включением в терапию препарата прямого противовирусного действия и специфического антицитомегаловирусного иммуноглобулина (анти-ЦМВ ИГ) в зависимости от клинической формы заболевания. Пролечено 62 ребенка: в первой группе был назначен противовирусный препарат (n = 21), во второй — анти-ЦМВ ИГ (n = 41). Проведен анализ клинико-лабораторных и инструментальных методов исследований, изучен катамнез детей до 3 лет. Статистический анализ выполняли с использованием программы SPSS Statistics и StatTech v. 3.1.6. Благоприятный исход зарегистрирован у 28,6% детей, пролеченных препаратом прямого противовирусного действия, и у 58,5% детей, пролеченных анти-ЦМВ иммуноглобулином. Вне зависимости от терапии доля практически здоровых детей к 3 годам жизни составила 50%. Большинство детей, включенных в исследование, терапию переносили удовлетворительно. Однако у 66% детей курс терапии противовирусным средством прямого действия был сокращен до 14 дней из-за проблем с венозным доступом, у 4,8% обнаружена тромбоцитопения, у 9,5% повышение активности трансаминаз. При сопоставлении исходов заболевания в зависимости от дня начала терапии статистически значимые различия удалось установить только при применении специфической противовирусной терапии (p = 0,044).

Ключевые слова: врожденная цитомегаловирусная инфекция, ганцикловир, гипериммунный анти-ЦМВ иммуноглобулин, исходы

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Congenital infectious diseases (CID) are second to hypoxia and asphyxia in the list of causes of morbidity and mortality of newborns. In the developed countries, cytomegalovirus (CMV) is the main etiological factor of CIDs that can lead to disability [1]. Every third to sixth newborn out of 1000 live-born children receives CMV ante- or intranatally, and 20–25% of them exhibit symptoms at birth and/or long-term consequences [2]. This has a significant impact on public health.

The clinical picture of congenital cytomegalovirus infection (CMVI) varies widely from no signs thereof to a potentially life-threatening generalized form of the disease involving damage to the central nervous system (CNS), liver, bone marrow, gastrointestinal tract, and other organs [3]. The therapy tactics and monitoring depend on the additional tests and examinations that clarify the form of congenital CMVI and follow etiological verification of the diagnosis.

Today, ganciclovir and valganciclovir are the only direct-acting antivirals used to treat congenital CMVI. Numerous studies have confirmed the positive effect of these drugs on the clinical course of the disease, as well as reliable normalization of indicators learned with laboratory tests, improvement of the weight and height parameters, improvement of hearing, neurological status, and reduction of the CID-caused mortality [4, 5].

However, ganciclovir may cause adverse events, such as neutropenia, leukopenia, anemia, thrombocytopenia, increased creatinine levels, liver transaminase activity, etc. [4]. To children in their first years of life, this drug can be prescribed only off label, after a council that involves more than three specialized medical professionals once parents of the child in question have signed the informed consent form. Oral forms of valganciclovir (suspension, syrup) are not registered in the Russian Federation (RF).

Hyperimmune anticytomegalovirus immunoglobulin (anti-CMV IG) is another CMVI treatment option. It is a well-tolerated drug, however, to date, its high therapeutic efficacy has only been proven in subclinical and mild forms of congenital CMVI in children [6]. Anti-CMV IG as the sole drug is not indicated for children with clinically pronounced congenital CMVI that can cause severe consequences or death [7].

Today, there are no absolutely effective and safe antiviral therapy against congenital CMVI. This subject requires research efforts, including those designed to study long-term consequences of the disease against the background of antiviral therapy regimens.

The purpose of this work is to investigate the long-term consequences of congenital CMVI depending on the severity of the disease and the etiotropic therapy.

METHODS

This retrospective study examined the results of treatment of 62 children with congenital CMVI, based on their records from the Pediatric Research and Clinical Center of Infectious Diseases of the Federal Medical Biological Agency of Russia. The records covered the period from January 2017 to December 2022. Primary documentation (inpatient and outpatient medical records) provided data for the analysis of clinical manifestations, laboratory test results and long-term consequences in the observed children. The follow-up period ranged from 1 to 3 years. Most (69.4%) of the children were followed up for three years, 24.2% — for two years, and 6.5% for 1 year.

Criteria for inclusion in the study: confirmed congenital CMVI; no \perinatal HIV contact.

Criteria for exclusion from the study: HIV-positive mother; severe congenital disorders; chromosomal and/or genetic syndromes.

Congenital CMVI was diagnosed when the disease manifested clinically and the child's blood plasma sampled in the first three weeks of life carried DNA of CMV, as per clinical recommendations [3].

AmpliSense®CMV-FL reagents (Central Research Institute of Epidemiology of Rospotrebnadzor, Russia) and PCR tests (minimum sensitivity — 400 copies/ml) enabled detection of CMV's genetic material (DNA) in blood plasma, urine and saliva.

All patients underwent a history and physical examination, their complaints were analyzed. Examination involved registration of the following data: gender, gestation period at birth, course of pregnancy and childbirth, condition at birth and during the neonatal period, age at diagnosis, physical and psychomotor development, dynamics of the disease. Laboratory and instrumental tests were carried out in accordance with clinical recommendations [3].

All the children were examined by an ophthalmologist, a neurologist and a surdologist. The patients underwent neurosonography (NSG) and ultrasound examination of the heart, abdominal cavity and kidneys; Mindray M7 (Mindray; China) and Logiq E9 (GE Medical Systems Ultrasound and Primary Care Diagnostics; USA) systems were used for this purpose. Given appropriate indications, some patients were prescribed magnetic resonance imaging (MRI) or computed tomography (CT) of the brain and abdominal cavity, and those with hepatitis had liver fibroelastography performed with Fibroscan® (model 502, Touch Echosens; France) in accordance with the standard operating procedures. METAVIR score [8] enabled determination of the stage of fibrosis.

Depending on the etiotropic therapy regimen, all participating children were divided into two groups: group 1 — children who received a direct-acting antiviral drug (DAAD) (ganciclovir, 6 mg/kg, IV, every 12 hours, course duration — 14–21 days), $n = 21$; group 2 — children who were prescribed an anti-CMV IG as the initial drug (1 ml/kg, IV drip, 6 administrations every 48 hours), $n = 41$. The authors of this work did not participate in the choice of drugs because treatment of the children began before their cases were transferred for supervisory control to the Pediatric Research and Clinical Center of Infectious Diseases. The medical documentation contained no information about the use of valganciclovir.

The outcomes of the congenital CMVI with damage to the CNS were evaluated under the pediatric outcomes scale, which is a modification of the Rankin, Fisher and Glasgow scales [9]. The scale factored in presence/absence of the neuropsychiatric deficit (in comparison with the age norm); 0 points meant a fully healthy condition, 5 points — fatal outcome (Table 1). The sums from 3 through 5 points were considered adverse outcomes.

In the cases when cerebral palsy was part of the disease's outcome, we used the GMFCS Scale (Gross Motor Function Classification System, enables assessment of the gross motor skills in cerebral palsy cases), with motor skills at level I, II and III thereunder considered benign outcomes, and levels IV and V — adverse outcomes.

For statistical analysis, we used SPSS Statistics (version 23) and StatTech v.3.1.6 (StatTech; Russia). To assess conformity of the quantitative indicators to the normal distribution patterns, we used the Shapiro-Wilk test for samples smaller than 50 and the Kolmogorov-Smirnov test for samples larger than 50. The values that did follow the normal distribution patterns, they were described using arithmetic means (M) and standard deviations (SD) with CI at 95%. Comparison of the two groups by a quantitative indicator with normal distribution, given equality of the variances, was done using the Student's *t*-test. The data

Table 1. Pediatric scale of outcomes of purulent meningitis

Point	Characteristic
0	Healthy
1	No significant deviations from the age norm in motor functions and intellectual development; mild neurological deficit that can be fully remedied. Complete socialization
2	Mild motor or sensory deficits and/or delayed psychomotor and speech development, necessitating complex rehabilitation; symptomatic epilepsy controlled with antiepileptic drugs. For children over 3 years of age — preserved motor activity and self-care ability, despite the persistent neurological deficit. Good socialization in the family, group of children (with a little irregular help from adults).
3	Delayed psychomotor development that cannot be corrected in full by the complex methods of rehabilitation; epilepsy, poorly controlled with antiepileptic drugs; need for constant help from the others. Socialization in specialized groups/institutions
4	Severe neuropsychiatric deficit. Need for permanent care, specialized (neuropsychiatric) medical assistance. Socialization impossible
5	Death

by category were given in absolute values and percentages. To compare percentages in the fourfold contingency tables, we used Fisher's exact test (with the expected event values below 10), and for multifold contingency tables — Pearson's chi-squared test (with the expected event values above 10); the comparison of binary indicators characterizing two related aggregates was done with the help of McNemar's test. Assessment of the prognostic significance of quantitative signs in prediction of a certain outcome relied on the ROC curves analysis. The dividing value of the quantitative marker at the cut-off point was determined by the highest value of the Youden's index. The differences between the studied indicators were considered statistically significant at $p < 0.05$.

RESULTS

Patient characteristics

The study included 62 children: 27 (43.5%) aged from 1 to 3 months, 35 (56.5%) — from 4 to 6 months. Boys made up 53.2% of the participants, girls — 46.8%. For 88.7% of the participants, the course of the antenatal period included adverse events: threat of termination in 17 (27.4%) cases; intrauterine growth restriction (IGR) in 12 (19.4%) cases, with premature infants suffering the condition twice as often as full-term babies (9.7% and 4.8% of cases, respectively; $p = 0.001$); pregnant mother having ARVI of varying severity in 41.9% of cases. During pregnancy, the mothers were not tested for CMVI. The majority of the participating children were full-term (64.5%; 40 children). The average birth weight was from 650 to 1914 g. The age of patients at the initial visit to the Center was 3.8 ± 3.2 months.

The clinical manifestations were very diverse (Fig. 1). Central nervous system was damaged in more than 60% of children, the conditions including meningoencephalitis in three (4.8%) of them, encephalitis in one (1.6%), developing hypertensive hydrocephalus syndrome in six (9.7%). Eighteen (29%) infants had enlarged liver, 9 (14.5%) — a combination of hepatomegaly and splenomegaly, and the rest had hyperfermentemia (from 2 to 20 norms due to ALT). Hemorrhagic syndrome was registered in 3.2% of the observed children with hepatitis. In 9.7%, direct bilirubin disrupted pigment metabolism 9.7%. Eye damage was diagnosed in 19.4% of infants, sensorineural hearing loss — in two (3.2%), neutropenia — in 32.2% of children (neutrophil level did not

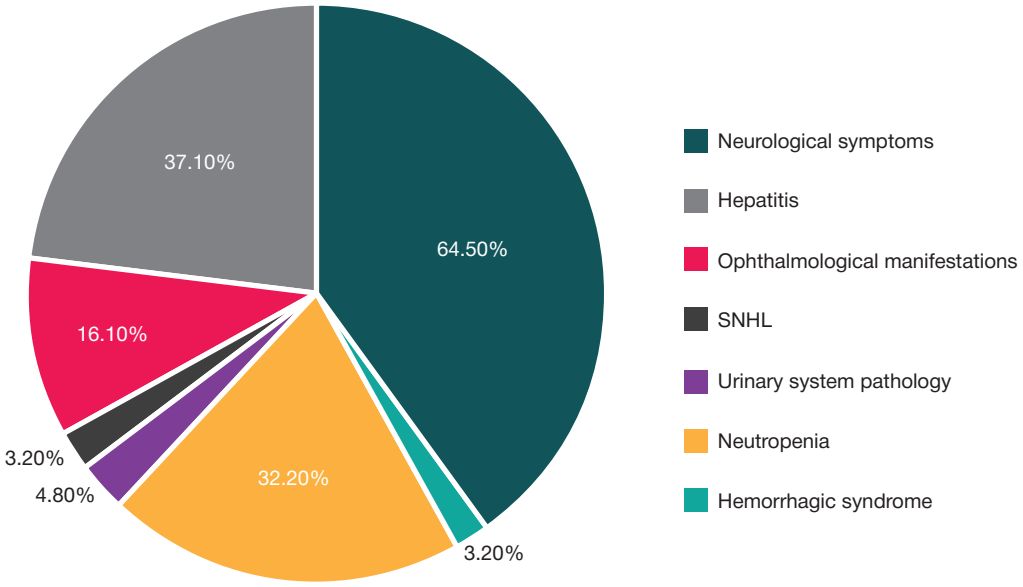

Fig. 1. Clinical manifestations in children with congenital cytomegalovirus infection

Table 2. Clinical manifestations in children with congenital cytomegalovirus infection, groups 1 and 2

Clinical manifestations	DAAD (n = 21)		Anti-CMV IG (n = 41)		Statistical differences between groups
	Abs.	%	Abs.	%	
Neurological symptoms	17	85.7	20	48.8	p = 0.005
Hepatitis	7	33.3	19	46.3	p = 0.177
Ophthalmological manifestations	3	14.3	5	12.2	p = 1.000
SNHL	1	4.8	1	2.4	p = 1.000
Urinary system pathology	0	0	3	7.3	p = 0.545
Neutropenia	5	23.8	15	36.6	p = 0.156
Hemorrhagic syndrome	2	9.5	0	0	p = 0.111

exceed 500/μl), and a combination of neutropenia and anemia was observed in 25.8% of the participants.

Children with congenital CMVI received the direct-acting antiviral drug if their CNS was severely damaged or there was combined damage to the CNS and other organs. Anti-CMV IG was used as a sole drug in mild cases with isolated manifestations (hepatitis, neutropenia) (Table 2); in that group, the dominating neurological symptom was hypoxic-ischemic perinatal encephalopathy.

The courses of the disease were identified based on the clinical recommendations [3]; in 58.1% and 12.9%, respectively, it took moderate and severe courses, in 17.7% and 11.3% of children — mild and subclinical.

Table 3 presents the results of examination of clinical manifestations of congenital CMVI depending on the course of the disease. Typically, severe course translated into damage to several organs, including CNS and liver. The prevailing disease associated with a mild course was hepatitis (91.7% of cases). In this study, only two children had sensorineural hearing loss; the infection course was moderate in them. As for neutropenia, it was registered in all mild course cases, 8.3% of moderate cases, and 62.5% of the severe course cases.

Therapy results

In our study, 21 children received DAAD (group 1), 41 children — anti-CMV IG (group 2).

Regardless of the type of therapy, the share of children that became healthy by the age of 3 was 50% of the entire sample. In group 1, 28.6% of the outcomes were benign, in group 2 — 58.5%. Mild neurological deficiency was observed in 17 children (27.4%), moderate deficit — in 6 (9.7%), gross organic deficit — in 8 (12.9%). Psychomotor retardation was diagnosed in 19 children (30.6%), and 6 (31.6%) children had cognitive impairments accompanied by various neurological syndromes (hypertensive hydrocephalus, convulsions, muscle tone disorder).

Six children (28.6%) from group 1 (DAAD) were diagnosed with cerebral palsy at the age of one year; it was the most severe form of motor disorders. By the GMFCS scale, 1 child out of these 6 had the motor functions of level III, 2 children — of level IV, and 4 children — of level V. Audiological examination revealed one child with 1st degree unilateral chronic sensorineural hearing loss.

In group 2 (anti-CMV IG), 31.7% of the participants (13 children) had psychomotor retardation, 12.2% (5 children) — convulsions, and one child (2.4%) was diagnosed with cerebral palsy, in this case the motor function disorders were of level II of the GMFCS scale, which is considered a benign outcome of the disease (Table 4).

Congenital CMVI can cause liver cirrhosis with subsequent fatal outcome. In our study, against the background of ongoing therapy, we observed normalization of the sizes of liver and spleen, as well as transaminase activity (Fig. 2), in all children (p < 0.05). Hepatitis was taking chronic course in four children, with one showing no signs of liver fibrosis, and three suffering this condition (stages 1–2).

According to the respective comparison, gestation period of newborns has no effect of the outcomes of congenital CMVI (p = 1.000). The chances of an adverse outcome of the congenital disease were equal in both groups (95% CI: 0.160–6.255).

Tolerability of DAAD amd anti-CMV IG therapy

There are known complications associated with use of DAAD, and yet, the children included in this study tolerated therapy

Table 3. Clinical manifestations of congenital cytomegalovirus infection depending on the course of the disease

Clinical manifestations	Mild		Moderate		Severe		Statistical differences between groups
	Abs.	%	Abs.	%	Abs.	%	
CNS	2	16.7	30	83.3	8	100	p = 0.001 (I + II)
Liver	11	91.7	10	27.8	3	37.5	p = 0.285
Organs of sight	1	8.3	7	19.4	2	25	p < 0.001 (II + III)
Hearing organs	0	0	2	5.6	0	0	
Kidneys	0	0	3	8.3	0	0	p < 0.001 (II + III)
Hematopoiestic organs	12	100	3	8.3	5	62.5	p < 0.001 (II + III)
Damage to more than two organs	2	16.7	18	50	8	100	p < 0.001 (II + III)
Total:	12	17.7	36	58.1	8	12.9	

Table 4. Neuropsychiatric deficit in children with congenital CMVI before and after DAAD therapy

Neuropsychiatric deficit against the age norm (according to the pediatric scale)	Before treatment		After treatment		Statistical differences between groups
	Abs.	%	Abs.	%	
Mild neurological deficit (1 point)	2	9.5	8	38.1	$p < 0.05$
Moderate neurological deficit (2 points)	0	0	2	9.5	$p < 0.05$
Gross neurological deficit (3-4 points)	16	76.2	8	38.1	$p < 0.05$

Table 5. Neuropsychiatric deficit in children with congenital CMVI before and after anti-CMV IG therapy

Neuropsychiatric deficit against the age norm (according to the pediatric scale)	Before treatment		After treatment		Statistical differences between groups
	Abs.	%	Abs.	%	
Mild neurological deficit (1 point)	0	0	14	34.1	$p < 0.05$
Moderate neurological deficit (2 points)	11	26.3	5	12.2	$p < 0.05$
Gross neurological deficit (3-4 points)	7	17.1	0	0	$p < 0.05$

satisfactorily. The main problem was hindered venous access, registered in 14 children (66%); their course of therapy was reduced to 14 days, but this did not prejudice the ultimate positive virological effect. Other side effects manifested in three children. One child (4.8%) with meningoencephalitis had thrombocytopenia, and his platelet level dropped below 50; one administration of DAAD was omitted from the course, then, when the platelet level returned to normal, it was resumed and completed. In two children (9.5%), transaminase activity was growing up (two-fold ALT maximum, 1.5 fold AAT maximum), but the situation did not require cancellation of the DAAD therapy. When the was over, transaminase activity normalized on its own.

Factors affecting the long-term results of DAAD anti-CMV IG therapy

A one-dimensional logistic regression model was used to analyze the factors associated with a benign or adverse outcome of congenital CMVI. The factors included in the univariate analysis were gestation period (full-term/premature), presence or absence of intrauterine growth retardation, adverse course of the antenatal period, course of the disease, specific therapy start date, damage to the organs (central nervous system, liver, organs of sight and hearing, hematopoietic organs), involvement of more than two organs in the infectious process.

Investigation of the effect of these factors revealed no associations with an adverse outcome of congenital CMVI (Table 6).

ROC analysis (Fig. 3) revealed that the probability of an adverse outcome is significantly lower when DAAD therapy starts in the first 3 months of the child's life. This pattern reaches statistical significance ($p = 0.044$; AUC = 0.759 ± 0.107 with 95% CI: 0.550–0.968; sensitivity — 80.0%, specificity — 72.7%).

The timing of initiation of the anti-CMV IG therapy (before or after the child turns 3-months-old) did not affect the overall frequency of pathological developments by the end of the follow-up period (up to 3 years of life) (Fig. 4; $p = 0.417$), but it significantly reduced the frequency of adverse neuropsychiatric outcomes (Table 5)

DISCUSSION

Clinical manifestations of congenital CMVI are diverse; the course may be severe, taking form of meningoencephalitis, cholestatic hepatitis, respiratory disorders and sensorineural hearing loss during the neonatal period, or mild, subclinical, with no such signs of conditions and accidental diagnosing later on [10–12]. Our study describes courses and outcomes of congenital CMVI in patients treated from January 2017 to December 2022 at the Pediatric Research and Clinical Center of Infectious Diseases of the Federal Medical Biological Agency of Russia; these patients received anti-CMV IG and DAAD. Most of the children (64%) were diagnosed with damage to the CNS. Majority of the studies addressing the subject conclude that such damage and neurosensory loss of hearing are currently the most common manifestations of congenital CMVI in children all over the world, including Russia.

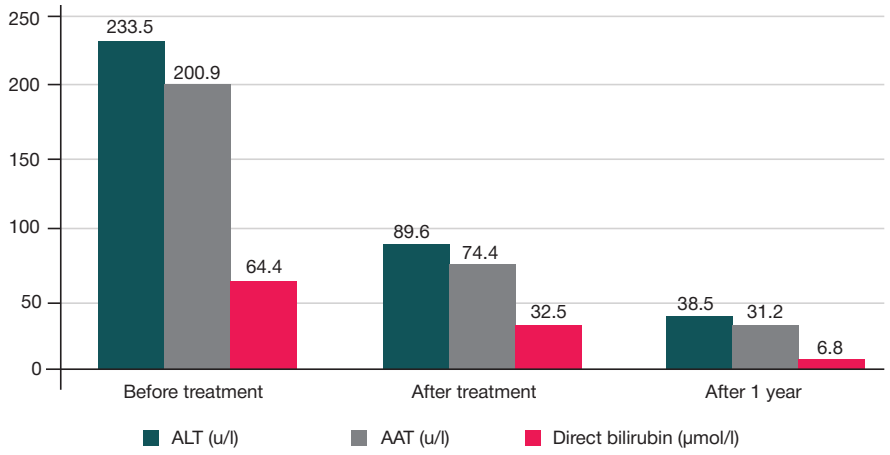

Fig. 2. Average values (μ) of ALT, AAT and direct bilirubin levels before therapy, after therapy and after 1 year

Table 6. Factors associated with an adverse outcome of congenital cytomegalovirus infection

№	Factor	*p*
1	Gestation period (full-term/premature)	0.312
2	Intrauterine growth retardation	0.438
3	Adverse antenatal course	0.834
4	Specific therapy start term	0.279
5	Course of the disease	0.52
6	CNS	0.187
7	Liver	0.297
8	Organs of sight and hearing	0.946
9	Involvement of more than 2 organs in the infectious process	0.266

In this study, meningoencephalitis was diagnosed in 4.8% of cases, encephalitis — in 1.6%, and other researchers put the incidence thereof at 3-32% of cases [13]; as for hypertensive hydrocephalus, it was registered in 9.7% of our patients, although other studies claim the incidence of this disorder to exceed 50% [14].

Hepatitis is a rather common disease for children with congenital CMVI, it is diagnosed in 17.4–26% of children [15, 16]; in 83% ALT exceeds 80 units/l, in 17% — 100 units/l [17]; there have been described cases of liver failure [18]. In this study, hepatitis was detected in 37.1% of the children, and a generally more severe course was notable; other characteristic features include the diagnosed combinations of hepatomegaly and splenomegaly (14.5% of cases), ALT and AAT values 2 to 20 times higher than normal, pigment metabolism disrupted by direct bilirubin (9.7% of cases), hemorrhagic syndrome (3.2% of cases).

Organs of sight were found damaged in 19.4% of the children, sensorineural hearing loss detected in two (3.2%), which is less frequent than in most other studies [19, 20]. Hematological pathology in the form of neutropenia was observed in 32.2% of children, a combination of neutropenia and anemia — in 25.8%.

Positively, this study disregarded many factors (e.g., gestation period in case of intrauterine infection) that affect prevalence and severity of the pathology in congenital CMVI cases, as well as the range of emerging long-term consequences and outcomes (Table 6).

Despite their toxicity, DAADs are used for etiotropic therapy against manifesting forms of the disease because of the high risk of death or subsequent disability it poses. Specific anti-CMV IG can be used as an additional etiotropic agent in severe congenital CMVI cases; if the course is mild or subclinical, anti-CMV IG can be the main drug of the regimen. The specifics of its use (doses, administration intervals, course duration), however, should be studied on a large sample of patients. In this study, we have shown that in mild cases, anti-CMV IG

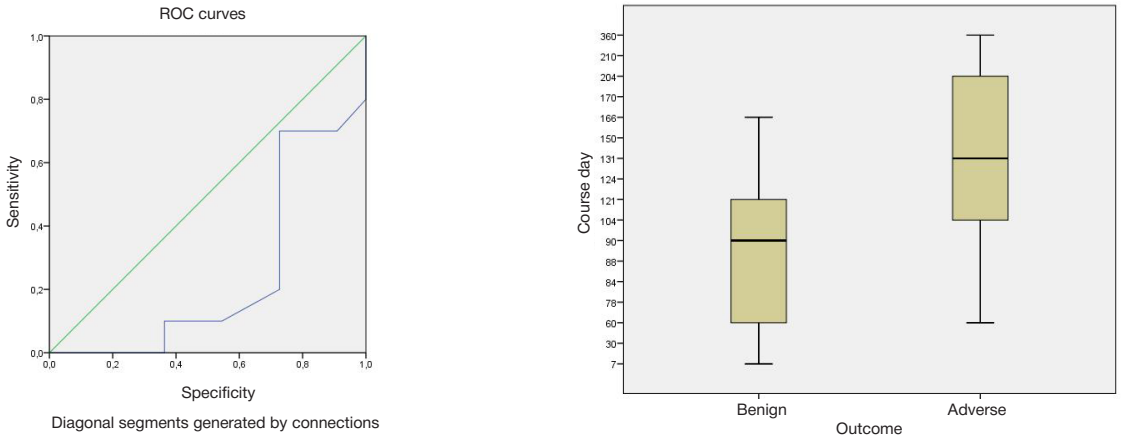

Fig. 3. ROC curve characterizing probability of an adverse outcome depending on the timing of DAAD therapy initiation

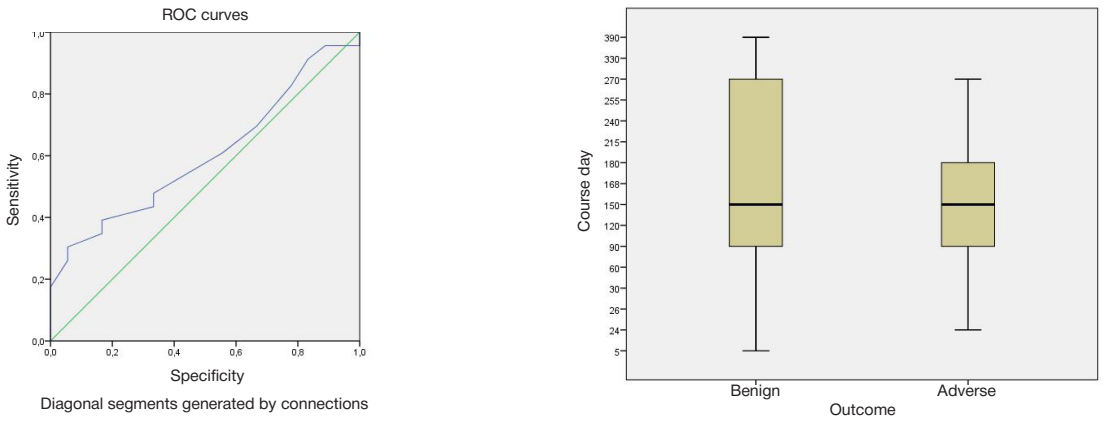

Fig. 4. ROC curve characterizing probability of an adverse outcome depending on the timing of anti-CMV IG therapy initiation

has a significant positive effect and relieves the symptoms of neuropsychiatric deficit; in particular, the drug completely eliminated gross neurological symptoms (Table 5). However, the data acquired should be tested on a larger number of observations in a randomized trial.

There is no doubt about value of early initiation of antiviral therapy in manifesting forms of CMVI [21]. However, the diagnosis is often made only 2–3 months after birth, and it is not always that doctor prescribe treatment in such cases. Unfortunately, most authors present isolated clinical cases describing the efficacy of DAAD and anti-CMV IG in children with congenital CMVI [22, 23]. This work shows that adverse outcomes in the form of cerebral palsy, psychomotor retardation, epilepsy, chronic sensorineural hearing loss, and disability since childhood were registered in 14.5% of children, which is much less than reported in observational studies where no antiviral drugs were used to treat congenital CMVI in children. We have not identified a single disability case caused by pulmonary fibrosis and liver cirrhosis as outcomes of congenital CMVI. A retrospective observational study of 2016 included 59 children with congenital CMVI who did not receive antiviral medicines; the authors of this study reported mental retardation in 94.4% of the patients, cerebral palsy in 38.9%, convulsive syndrome in 25.9% and hearing impairment in 66.7% [24]. There is a paper reporting the results of a three-month course of neocitotect given to 70 children with hypertensive hydrocephalus with congenital CMVI: the drug caused reduction of the size of ventricles in 28.5% of cases [25].

Tolerability of DAAD was a matter addressed specifically in the study. Apart from the hindered venous access, the drug was well tolerated. Only three children (14.2%) had side effects, thrombocytopenia and hyperfermentemia, that, however, did not lead to abortion of the course. In practice, limitations peculiar to the of DAAD are rooted not so much in their toxicity but in the need for frequent change of the infusion catheters [26].

CONCLUSIONS

Starting a DAAD therapy addressing severe and moderate congenital CMVI when the child is less then 3 months old significantly reduces the prevalence of all types of adverse outcomes, particularly, neuropsychiatric deficit; the effect is confirmed with a ROC analysis (by the end of the observation, gross deficit was twice as rare, and moderate manifestations of this type were completely eliminated). One of the possible reasons for persistence of adverse outcomes and long-term consequences - lack of prolonged valganciclovir course. There are mentions thereof in the medical documentation. In the context of this study, a course of anti-CMV IG prescribed to children with congenital CMVI manifesting mildly, regardless of the age of the child at its initiation (younger than 3 months, older than 3 months), was also significantly associated with alleviation of the neuropsychiatric deficit by the end of observation, and the gross neurological deficit was completely remedied. These data suggest that children with congenital CMVI can receive etiotropic therapy not only in the first weeks of life, but also later, if there are indications. Remembering that etiotropic therapy can be more successful when started early, it is necessary to conduct additional studies seeking to determine the critical period of a child's life within which initiation of such therapy is as effective as possible.

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