PREVALENCE OF CYTOMEGALOVIRUS INFECTION IN HOSPITALIZED INFANTS

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ABSTRACT

Data on cytomegalovirus infection (CMV) prevalence and course in hospitalized infants are rather scarce, obsolete and considerably inconsistent.

AIM: to determine the prevalence, rate of clinical manifestations, risk factors and predictive capacity of clinical manifestations of CMV infection in hospitalized infants during their first year of life.

PATIENTS AND METHODS: All 163 infants hospitalized in the Pediatric Ward for Nonrespiratory Pathology in a tertiary hospital were serologically screened for cytomegalovirus infection for 10 months. In infants up to 6 months old that were CMV IgG (+) and CMV IgM (-) we followed up the CMV IgG concentration or compared it with that of their mothers.

RESULTS: The CMV prevalence for the entire study sample was 33.1 ± 3.7% (54 seropositive out of 163 examined infants); in newborns it was 19.4 ± 6.7% (7 of 36), in infants aged 1-3 months – 23.8 ± 5.4% (15 of 63), in 4-6-month olds – 28.1 ± 8.1% (9 of 32), and in 7-12-month old – 71.9 ± 8.1% (23 of 32). The rates of clinically apparent infections in the respective groups was 33.3 ± 6.5%, 57.01 ± 20.2%, 53.3 ± 13.3%, 33.3 ± 16.6%, and 13.0 ± 7.17%. The overall rate of clinically apparent CMV infection in all 163 children was between 11.0 ± 2.5% and 17.2 ± 2.9%. The probability of CMV infection increased with age and duration of breastfeeding. Hepatitis, cerebral vasculopathy and pneumonia (alone or combined) turned out to be predictors of CMV infection, but none of these symptoms had a frequency greater than 22%.

CONCLUSIONS: We found a high rate of cytomegalovirus infections in hospitalized infants less than one year of age. This infection is the reason why at least 10% of the newborns and 12% of the children aged 1 to 3 months were hospitalized. The course was clinically apparent in over half of the infected children of up to 3 months of age.

Key words: cytomegalovirus, newborns, babies, prevalence rate, screening, clinical signs, risk factors

INTRODUCTION

Cytomegalovirus infection (CMV) is among the most common infections during the first year of life.1-3 The population rate of congenital CMV infection ranges from 0.04% to 2.2% depending on geographical and socio-economic factors.2,4,5 Studies conducted in Bulgaria between 1992 and 1997 showed the congenital CMV infection to have a relatively high incidence rate (2.4%) in newborns.6 However, most of the infections occurring in the first year of life are postnatal or perinatal as a result of which more than one-third of children are CMV seropositive at about 12 months of age.7,8

In clinical practice, risk assessment for complications, indications for antiviral treatment and resource planning are based on data about the CMV infection rate in hospitalized children. These data differ from the population data, and very often are scarce, obsolete and considerably inconsistent - CMV is found in 3.0% to 9.8% of all hospitalized infants9,10 and in 38.2% to 80.9% of the children in the first three months after birth.11,12 There are very little actual data about the prevalence, symptoms and risk factors for the infection in hospitalized infants.

Objective: the present study aims at determining the prevalence rate, the rate of clinical manifestation,
risk factors and predictive capacity of the clinical manifestations of CMV infection during the first year of life of hospitalized infants.

**PATIENTS AND METHODS**

Design of the study: open epidemiological cohort study with serological screening at baseline.

*Inclusion criteria*: any hospitalized infant within 12 months of age admitted to the Infant Ward of the Division of Pediatric Neurology, Gastroenterology and Medical Genetics at the Department of Pediatrics and Genetic Diseases of St George University Hospital, Plovdiv. The clinic is ranked a hospital for tertiary care providing health care services for the regions of Plovdiv, Pazardzhik, Haskovo, Kurdzhali and Smolyan.

*Exclusion criteria*: Unavailable serological examination of the infant, no parental consent for inclusion of the infant into the study.


*Serodiagnosis of CMV infection*: Serological testing to detect CMV IgM and determination of CMV IgM antibodies concentration at admission to the Ward (EIA-1796 and EIA-1797, DRG International Inc., USA). In IgM negative - IgG positive infants at age 3-6 months concentration of maternal IgG was measured, while in infants with the same serological status at age 0-3 months the concentration of their IgG was retested 1-2 months after baseline.

**Classification of the CMV infections**

*Present infection* – if the child is CMV IgM positive; if the child is CMV IgG positive after 6 months of age; if the CMV IgG concentration increases or is persistent; if the child’s CMV IgG concentration is higher than that of the mother.

*Possible infection* – in 0-6-month-old children that are CMV IgM-negative and CMV IgG-positive and there is no monitoring of CMV IgG or comparison with the maternal CMV IgG.

*No infection* – if there are no CMV IgM and CMV IgG; if only CMV IgG is detected in infants up to 6 months of age with decreasing concentration and/or lower concentration than the maternal CMV IgG.

**CMV infections classified by clinical course**

*Symptomatic infection* - if there are symptoms for congenital or acquired CMV infection (see Addendum), after ruling out other possible pathological conditions.

*Concomitant infection* – if there are symptoms of CMV infection, but in addition there are other etiological factors that may account for these symptoms (e.g., hypoxic-ischemic encephalopathy).

*Asymptomatic infection* - if the infection has been diagnosed in a child hospitalized for other reasons and not having symptoms indicative of CMV infection (e.g., obstetric brachial plexus paralysis in a child.)

*Age groups*: newborns (0-1 month of age), 1-3 months old, 4-6 months old, and 7-12 months old.

**Risk factors for CMV infection**

The admission history included information about the patient’s age, length of breastfeeding (weeks), total duration of previous hospitalizations, prematurity or low weight at birth, transfusion of blood or its derivatives, whether or not the infant has been reared in an orphanage, low family income (as self-reported by the family or if the baby has a single female parent or an unemployed father).

*List of the common CMV symptoms searched on admission to the Ward*: hepatosplenomegaly, icterus, hepatitis, abnormal muscle tone, developmental delay (DD), seizures, encephalitis, microcephaly, hypacusis, visual deficit, cerebral vasculopathy, cerebral calcifications, chorioretinitis, pneumonia, fever longer than 7 days, thrombocytopenia, hemolytic anemia and lymphocytosis (see Addendum).

*Procedures in the Ward*: Passport data and information regarding patients’ history, symptoms of CMV infection and risk factors were documented in a specially designed card upon admission to the Ward. CMV IgM and CMV IgG were tested in the first blood sample taken after admission. Based on the results we got, within 72 hours we assessed whether it was necessary to study the maternal CMV IgG or to follow-up the child’s CMV IgG as instructed in the algorithm discussed earlier.

**Statistical analyses** included the analysis of variance, the t-test, the Fisher’s exact test, $\chi^2$, the Kruskal-Wallis test, dispersion analysis, ROC curves and logistic regression models. $P > 0.05$ was accepted as level of significance for the null hypothesis. All data were analysed using SPSS (version 13).

The study was approved by the Science Ethics Committee at Plovdiv Medical University.

**RESULTS**

During the study period 169 children aged up to 356 days were admitted to the Ward. Six children were excluded from the study: 5 due to failed serological
testing for CMV and 1 because of parental refusal to participate. The remaining 163 children were the units of observation. Of these, 99 were boys (60.7 ± 3.8%), and 133 lived in urban settings (81.5 ± 3.0%). The most common reasons for admission to the Ward were presence of hepatosplenomegaly (in 36 infants), abnormal muscle tone (in 33 infants), icterus (in 28), pneumonia (in 21), developmental delay (in 20), hepatitis (in 19), seizure (in 16 infants) and some others, some children being hospitalized for more than one reason. One hundred and eighteen children were breastfed, 52 children had been hospitalized previously, 22 were preterm babies or had intrauterine hypotrophy, 17 received blood and blood products, 4 were reared in an orphanage and 47 were born to low-income families.

CMV infection was found in 54 children (33.1 ± 3.7%). There was no infection in 101 children (62 ± 3.8%), while 8 (4.9 ± 1.7%) were identified as having a possible infection.

We detected CMV infection in 7 (19.4 ± 6.7%) of the 36 one-month-old newborns, in 15 (14.8 ± 5.4%) of the 63 one-to-three-month old infants, in 9 (28.1 ± 8.1%) of the 32 children 4-6-month of age and in 23 (71.9 ± 8.1%) of the 32 children 7-12-month old. The number of children with possible infection was 3, 4, 1, and 0 in the respective age periods, and with no infection – 26, 33, 22 and 9, respectively. The increase of the infection rate in children with age was statistically significant ($\chi^2 = 28.78; p < 0.0001$) (Fig. 1).

CMV infection was classified by clinical course in 54 children as follows: symptomatic in 18 (33.3 ± 6.5%), concomitant infection in 10 children (18.5 ± 5.3%) and asymptomatic in 26 children (48.1 ± 6.8%).

The infection was symptomatic in 4 (57.01 ± 20.2%) of the 7 infected newborns, in 8 (53.3 ± 13.3%) of the 15 infected infants at the age of 1-3 months, in 3 (33.3 ± 16.6%) of the 9 infected children 4-6 months of age, and in 3 (13.0 ± 7.17%) of the 23 infants with CMV infection of 7-12 months of age. The infants with concomitant infection were 2, 3, 0, and 5 in the respective age groups, and with asymptomatic infection – 1, 4, 6 and 15, respectively. The decrease of the number of cases with a symptomatic course accompanied with increase of asymptomatic infections with age was statistically significant ($\chi^2 = 13.64; p < 0.05$) (Fig. 2). No correlation was found between gender and the presence of CMV infection or its course ($p > 0.05$).

Analysis of the suspected risk factors for CMV infection revealed that the probability of infection increases with age and with the duration of breastfeeding (Table 1). There were no children in the study that were fed with thawed breast milk. We found no correlation between the presence of CMV infection and the length of hospital stay, premature birth, transfusion of blood and its products, rearing in an orphanage or low family income. None of these risk factors, with the exception of age, correlated with the symptomatic or asymptomatic course of the infection.

![Figure 1. Distribution of CMV infection by age (n = 163).](image1)

![Figure 2. Age-related course of the CMV infection (n = 54).](image2)
The analysis of the available clinical and paraclinical data at admission to the Ward showed that only hepatitis correlated significantly with presence of CMV infection (Table 2).

We performed a multifactorial multistage logistic regression analysis to assess the predictive value of symptoms at admission to the Ward to identify CMV infection (Table 3). The factors included are

Table 1. Risk factors for CMV infection in the first year of life (n = 163)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Presence of CMV infection (n = 54)</th>
<th>No CMV infection (n = 101)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days), $\bar{x} \pm SD$</td>
<td>164.48 ± 111.27</td>
<td>89.98 ± 82.33</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean duration of breastfeeding (weeks), $\bar{x} \pm SD$</td>
<td>13.67 ± 9.53</td>
<td>6.78 ± 6.54</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean duration of hospital stay (weeks), $\bar{x} \pm SD$</td>
<td>3.71 ± 4.65</td>
<td>2.48 ± 1.12</td>
<td>N. S.</td>
</tr>
<tr>
<td>Prematurity or low birth weight, % ± Sp</td>
<td>11.11 ± 4.28%</td>
<td>14.43 ± 3.57%</td>
<td>N. S.</td>
</tr>
<tr>
<td>Infants receiving bioproducts, % ± Sp</td>
<td>9.4 ± 4.0%</td>
<td>11.6 ± 3.2%</td>
<td>N. S.</td>
</tr>
<tr>
<td>Infants reared in orphanages, % ± Sp</td>
<td>1.85 ± 1.83%</td>
<td>2.97 ± 1.69</td>
<td>N. S.</td>
</tr>
<tr>
<td>Families with low income, % ± Sp</td>
<td>33.3 ± 6.42%</td>
<td>26.6 ± 4.56%</td>
<td>N. S.</td>
</tr>
</tbody>
</table>

Table 2. Available clinical and laboratory data at admission to the Ward

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Presence of CMV infection (n = 54)*</th>
<th>No CMV infection (n = 98)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>n = 17</td>
<td>n = 19</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>12</td>
<td>7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Abnormal muscle tone</td>
<td>10</td>
<td>23</td>
<td>N. S.</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>9</td>
<td>11</td>
<td>N. S.</td>
</tr>
<tr>
<td>Seizures</td>
<td>5</td>
<td>11</td>
<td>N. S.</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0</td>
<td>2</td>
<td>N. S.</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>1</td>
<td>1</td>
<td>N. S.</td>
</tr>
<tr>
<td>Hearing deficit</td>
<td>0</td>
<td>0</td>
<td>N. S.</td>
</tr>
<tr>
<td>Visual deficit</td>
<td>1</td>
<td>2</td>
<td>N. S.</td>
</tr>
<tr>
<td>Cerebral vasculopathy</td>
<td>5</td>
<td>4</td>
<td>N. S.</td>
</tr>
<tr>
<td>Cerebral calcifications</td>
<td>1</td>
<td>0</td>
<td>N. S.</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>0</td>
<td>1</td>
<td>N. S.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>10</td>
<td>N. S.</td>
</tr>
<tr>
<td>Fever for more than 7 days</td>
<td>2</td>
<td>1</td>
<td>N. S.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>N. S.</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>0</td>
<td>1</td>
<td>N. S.</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>0</td>
<td>0</td>
<td>N. S.</td>
</tr>
</tbody>
</table>

* There are no data for one child with CMV infection and 3 children without CMV infection.
Prevalence of Cytomegalovirus Infection in Hospitalized Infants

Table 3. Multifactorial logistic model for assessment of the effect of independent factors for CMV infection in the first year of life

<table>
<thead>
<tr>
<th>Factor</th>
<th>β coefficient</th>
<th>S. E.</th>
<th>p</th>
<th>OR</th>
<th>95.0% confidence interval for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.00</td>
<td>0.000</td>
<td>1.01</td>
<td>1.01 - 1.02</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2.00</td>
<td>0.58</td>
<td>0.001</td>
<td>7.42</td>
<td>2.38 - 23.12</td>
</tr>
<tr>
<td>Cerebral vasculopathy</td>
<td>1.41</td>
<td>0.80</td>
<td>0.077</td>
<td>4.11</td>
<td>0.86 - 19.70</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.37</td>
<td>0.55</td>
<td>0.013</td>
<td>3.95</td>
<td>1.34 - 11.68</td>
</tr>
<tr>
<td>Constant</td>
<td>-2.45</td>
<td>0.41</td>
<td>0.000</td>
<td>0.09</td>
<td>-</td>
</tr>
</tbody>
</table>

The CMV infection prevalence in hospitalized infants up to one year of age is 33.1±3.7% (95% CI = 25.8 ÷ 40.3%). It is higher than prevalence rate (16%) found in a pediatric chronic care unit in the United States14, but lower than the data obtained in a serological screening in a hospital in Thailand, showing a rate of over 60%11.

The prevalence we found (19.5%) in the first month of life is similar to the results acquired through analysis of viral excretion: 15.7% in Hungary10 and 12.6% in Egypt15, or by screening for CMV IgM in India – 12.5%17. Data from a Neonatal Unit in the United States showed a lower prevalence (3.0-5.7%).9 Judging from literary evidence for the occurrence of own CMV antibodies after 4 weeks of infection1, we can assume that the majority of infections in newborns are congenital, and therefore increasing the risk for neurodevelopmental complications. The fact that CMV infection was found in almost one-fifth of the newborns in the study sample indicates the social significance of the problem.

Based on data reported in the relevant literature about a greater population rate of perinatal infection (40-60% in breastfed newborns)1,3,15 in comparison with the rate of congenital infection, and of a minimum incubation period of one month1 we can assume that most of the infections after one month of age are acquired during and after birth. Their rate in the present study is close to 25% and is less than the rate of 38.6% for the perinatal cytomegalovirus infection in a Brazilian hospital.12

A prevalence rate of 72% in the second six months is comparable with the results from a previous study conducted in Bulgaria13, while the data from other countries range from 38.2% in Australia7 to 93.3% in Turkey8.
The overall rate of clinically apparent CMV infection in hospitalized infants up to one year of age was between 11.0 ± 2.5% and 17.2 ± 2.9% (18 of 163 or 28 of 163 children) depending on whether or not the 18 infants with symptomatic infection are accompanied by the 10 infants with a concomitant infection. No comparable data were found in the available literature.

We found a high rate of symptomatic CMV infection in hospitalized children in the first four months of life (12 out of 22 infected, 54.5% ± 10.9%). According to population studies congenital and perinatal infections are symptomatic in about 10% of cases. Hospital-based studies have reported a higher rate – 12.5 to 23%. A Nagy et al. found 6 children with clinical manifestations of infection out of 10 newborns with congenital CMV infection in Hungary. T Tomasik et al. also found a higher rate of infections running a symptomatic course (16 out of 27 (59%) infected in a neonatal intensive care unit). It can be assumed that the higher rate of symptomatic infections in this study, as well as in the latter two cited studies, is due to the specific pathology managed in the Ward where the study was conducted. It is also possible that other risk factors, still unknown, to increase the clinical severity of the infection.

On the basis of the rate of CMV infections and the rate of symptomatic cases (after excluding infants with concomitant infection), it can be concluded that the CMV infection was the reason for hospitalization of at least 10% of newborns and 12% of children aged 1-3 months.

The greater age and the longer breastfeeding were confirmed as risk factors for CMV infection, which is consistent with the literature data, although the data regarding the risk in breastfed premature infants are controversial. Duration of previous hospitalizations did not prove to be a risk factor in this study in spite of the literary data. Prematurity is a risk factor according to some authors, but this finding is refuted by others, as do the authors of the present study. Low family income, rearing in an orphanage and infusion of bioproducts, which showed no correlation with CMV infection in the present study, are risk factors according to some authors but not to others.

The analysis of the clinical and paraclinical data which are the reason for hospitalization or are established during the first examination in the hospital aims to determine which symptoms have a reliable predictive value for CMV infection so that they can serve as indications for timely diagnostic tests for CMV. Although hepatitis, cerebral vasculopathy and pneumonia are the commonly recognized manifestations of CMV infection, none of these symptoms show a rate greater than 22%. It turned out that the sensory and hematological disorders, although more specific, are rare or established only during hospitalisation of the children, while very common disorders such as hepatosplenomegaly, abnormal muscle tone and developmental delays do not have sufficient specificity.

CONCLUSIONS

We found a high prevalence rates of cytomegalovirus infection in hospitalized infants less than 1 year of age. This infection is the reason for hospitalization for at least 10% of the newborns and 12% of the children aged 1 to 3 months. The course of the condition is clinically apparent in over half of the infected children of up to 3 months of age. Significant risk factors for CMV infection are greater age and prolonged breastfeeding. Hepatitis, cerebral vasculopathy and pneumonia (alone or in combination) proved to be predictors of CMV infection, but none of the symptoms had a rate exceeding 22%.

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ADDENDUM

A list and criteria of the studied common symptoms of cytomegalovirus infection.

1. Prematurity and/or low birth weight: birth weight under 2500 g or gestational age less than 38 weeks.
2. Hepatosplenomegaly: the liver is palpable at more than 3 cm along the midclavicular line and/or has thicker than soft and elastic consistency and/or the spleen is palpable at more than 1 cm below the costal margin.
3. Icterus: neonatal hyperbilirubinemia (> 256 μmol/l) or prolonged icterus (bilirubin > 21 mmol/l after 21 days from birth).
4. Hepatitis: ultrasound confirmed hepatomegaly and/or abnormal density of the liver combined with persistently elevated transaminases for at
least 1 week (AST > 43 U/l up to 6 months of age and > 35 U/l from 6 to 12 months of age and/or ALT > 45 U/l).

5. Abnormal muscle tone: muscle hypotonia and/or hypertention, diagnosed on the basis of more than 1 sub-optimal value of passive motion angles and/or more than one abnormal posture in the kinesiologic study.


7. Seizure: clinically manifested sudden change in the muscle tone, behavior and/or consciousness.

8. Encephalitis: altered consciousness accompanied by seizures and/or paresis during or after a systemic infection or neuroinfection confirmed by CSF pleocytosis, elevated CSF immunoglobulins or by virological CSF examination.

9. Microcephaly: a head circumference less than 2 SD as by the reference ranges of the official bulletin of the Ministry of Health.

10. Auditory deficit: no audio-palpebral reflex and, after 2 months of age – absence of auditory concentration.

11. Visual deficit: absence of visual concentration after 1 month of age and of visual tracking after 2 months of age.

12. Cerebral vasculopathy by transfontanellar ultrasound – hyper-echogenic vessels.

13. Cerebral calcification: confirmed by CT study.


15. Pneumonia: radiographically confirmed.

REFERENCES


РАСПРОСТРАНЕННОСТЬ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ СРЕДИ ГОДОВЫХ ДЕТЕЙ

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РЕЗЮМЕ

ВВЕДЕНИЕ: Данные о частоте и течении цитомегаловирусной (СМВ) инфекции среди госпитализированных детей недостаточны, неактуальны и значительно варьируют.

ЦЕЛЬ: Исследовать распространенность, частоту клинического проявления, факторы риска и предиктивную способность клинических проявлений СМВ инфекции в течение первого года жизни госпитализированных детей.

ПАЦИЕНТЫ И МЕТОДЫ: В течение 10 мес. проводили серологический скрининг относительно цитомегаловирусной инфекции всем 163 детям, госпитализированным в педиатрическое отделение нереспираторной патологии (больница третьего уровня компетентности). У детей до 6-месячного возраста с CMV IgG (+) и CMV IgM(-) прослежена концентрация CMV IgG или она сравнивается с материнской.

РЕЗУЛЬТАТЫ: Распространенность СМВ для всей группы – 33.1 ± 3.7% (54 серопозитивные из 163 обследованных); только для новорожденных – 19.4 ± 6.7% (7 из 36); в возрасте 1-3 мес. – 23.8 ± 5.4% (15 из 63); в возрасте 4-6 мес. -28.1 ± 8.1% (9 из 32); в возрасте 7-12 мес. -71.9 ± 8.1% (23 из 32). Частота клинически проявленной инфекции относительно общего числа серопозитивных в соответствующих группах – 33.3 ± 6.5%, 57.1 ± 20.2%, 53.3 ± 13.3%, 33.3 ± 16.6% и 13.07 ± 7.17%. Общая частота клинически проявленной инфекции среди всех обследованных 163 детей варьирует между 11.02 ± 2.5% и 17.2 ± 2.9%. Вероятность заражения показывает нарастание с возрастом и с продолжительностью кормления грудью. Гепатит, мозговая васкулопатия и пневмония (самостоятельно или в комбинации) оказались прогностическими факторами СМВ инфекции, но ни один симптом не показал частоту выше 22%.

ВЫВОДЫ: Установлена высокая частота цитомегаловирусной инфекции среди госпитализированных детей годового возраста. Инфекция является причиной госпитализации приблизительно 10% новорожденных и 12% детей в возрасте от 1 до 3 мес. Течение клинически проявлено у большей части зараженных до трехмесячного возраста.
