CLINICAL, SUBCLINICAL FEATURES AND RESULTS OF TREATMENT OF CYTOMEGALOVIRUS HEPATITIS IN CHILDREN

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ABSTRACT

Objective: *To describe the clinical and subclinical characteristics of hepatitis in children due to viral cytomegalo-infection and to comment on the results of treatment of hepatitis in children due to viral cytomegalo-infection at the National Children's Hospital.*

Research object and method: *Retrospective - prospective study,describing 89 pediatric patients 1-12 months diagnosed with Cytomegalovirus hepatitis and treated at the National Children's Hospital during the period from 01/01/2020 - 30/06/2022.*

Result: *89 patients with CMV hepatitis were followed for 6 months with the following rates: The average age of patients was 2.17 ± 1,596 months, and the ratio of males to females (2.5 : 1), jaundice 86.5%, hepatomegaly 64.0%, feces of silver color 52.8%, dark urine 44.9%, subcutaneous hemorrhage 4.5%. Most transaminases increase slightly and rarely exceed 400U/L. Direct billirubin increased by 91.2%. 66/89 are eligible for antiviral therapy with ganciclovir/ Valganciclovir. Improvement in liver damage was 90.9% and nocomplications accounted for 90.9%.*

Conclusion: *Most patients have good results after treatment. However, it is necessary to detect and treat in time to limit the severe damage caused by CMV.*

Keywords: *hepatitis, Cytomegalovirus*

I. INTRODUCTION

Cytomegalovirus (CMV) infection in children is a diverse and complex disease, ranging from asymptomatic to severe and life-threatening complications such as gastrointestinal, cardiovascular, hepatic and neurological manifestations, etc. CMV hepatitis is one of the most common lesions, which can progress to progressive liver disease, portal hypertension and cirrhosis, sometimes leading to death [1]. Not only causing acute lesions, CMV can also cause long-term sequelae such as deafness, mental retardation and congenital blindness.

Studies on CMV in children in Vietnam are currently very limited and the indications for antiviral treatment are not consistent. Therefore, I conducted the study: **"Clinical, subclinical features and results of treatment of cytomegalovirus hepatitis in children"** with the following research objectives:

1. Describe the clinical and subclinical features of cytomegalovirus hepatitis in children at the National Children's Hospital

2. Comment on the treatment results of cytomegalovirus hepatitis in children at the National Children's Hospital

II. RESEARCH SUBJECTS AND METHODS

2.1. Research subjects

Including all children aged 1-12 months diagnosed with CMV hepatitis at the National

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Children's Hospital from January 1, 2020 to June 30, 2022.

Patient inclusion criteria

- Evidence of acute CMV infection:

• Detect CMV antigen in blood specimens by PCR gene amplification reaction. And

• There is IgM - CMV antibody in blood specimens by ELISA technique.

- There is evidence of liver damage in subclinical tests: AST, ALT ≥ 80 IU/L [2]

Exclusion criteria:

- Hepatitis due to other causes: Metabolic disorders, congenital biliary atresia, evidence of liver damage due to other viral infections

- Patients with complex congenital diseases, patients after organ transplantation, after bone marrow transplantation, after chemotherapy

- Patients with congenital or acquired immunodeficiency.

2.2. Time and location of the study

Research location: National Children's Hospital

Time: The study was conducted from January 1, 2020 to June 30, 2022

2.3. Research methods

Retrospective - prospective, descriptive study from January 1, 2020 to June 30, 2022.

2.4. Sample size and sampling method

Sample size: Select all eligible patients to participate in the study.

Sampling method: Select convenient samples that meet the criteria for disease selection.

2.5. Research variables

Basic information of the research subjects: Basic data collected included demographics, maternal history, child history, clinical symptoms, subclinical tests, neurological imaging, and eye and hearing examinations. Liver function results, CMV PCR, and post-treatment complications.

2.6. Testing techniques applied in the study

CMV-IgM ELISA test and real-time CMV PCR from blood specimens.

2.7. Data processing and analysis

Quantitative data were checked, cleaned, coded, and entered using Epidata 3.1 software, then statistically processed using SPSS 20.0 software.

Based on the tests, the patients in the study group were divided into two groups.

+ Group without antiviral treatment:

Including patients with at least 1 of the following 2 criteria

- Negative CMV IgM antibody test

- Real time - CMV PCR in blood specimens below 5000 copies/ml

Patients in this group will only receive symptomatic supportive treatment

+ Group with antiviral treatment

- CMV IgM antibody test

- Real time - CMV PCR in blood specimens ≥ 5000 copies/m

Grouping to evaluate treatment effectiveness

Good prognosis group	Intermediate prognosis group	Poor prognosis or complication group
- CMV PCR < 1,000 Copies/ml after 21 days - Liver function recovered well after treatment - No severe CMV lesions	- CMV PCR ≥ 1,000 Copies/ml after 21 days - Liver function improved after treatment - No severe CMV lesions	- CMV PCR ≥ 1,000 Copies/ml after 21 days - Poor or no improvement in liver function after treatment - Severe CMV lesions

III. RESEARCH RESULTS

3.1. General Characteristics

Table 1. General information of the research subjects

Contents	Quantity	Rate %
Average age (n=89)	**2.1 ± 1.6 months**	
1 - <3 months	78	87.6
> 3 - 12 months	11	12.4
Gender (n=89)		
Male	64	71.9
Female	25	28.1
Birth weight (n=88)		
< 2500 grams	18	20.5
≥ 2500 grams	70	79.5
Delivery method (n=88)		
Vaginal delivery	50	56.8
Cesarean section	38	42.2
Birth order (n=88)		
First child	42	47.8
Second child and above	46	51.2
Nutrition (n=89)		
Breastfeeding	37	41.6
Formula	18	20.2
Mixed	34	38.2

Comments: The average age of patients was 2.1 ± 1.6 months, 87.6% were from 1 to under 3 months old, male accounted for 71.9%. Birth weight ≥ 2500g and gestational age ≥ 37 weeks accounted for a fairly high proportion (79.5% and 81.8% respectively), vaginal delivery (56.8%), number of breastfed children (41.6%), first child (47.8%).

3.2. Clinical and subclinical features of liver damage due to CMV infection

3.2.1. Clinical features

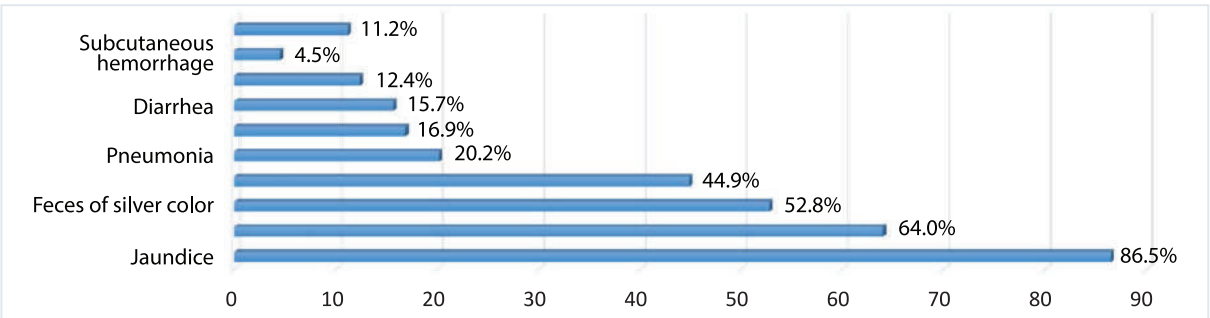

Chart 1. Characteristics of clinical symptoms of patients upon admission

Comments: The most common manifestations were jaundice (86.5%), hepatomegaly (64%) and feces of silver color (52.8%). Fever, pneumonia and diarrhea accounted for 12.4%, 20.2% and 15.7%, respectively. The least common manifestation was subcutaneous hemorrhage (4%).

3.2.2. Subclinical features

Table 2. Characteristics of hematological changes of patients upon admission (n=89)

Indicators	n	%
Leukocytes (thousand/mm3)	**11.4 ± 3.5**	
Decreased < 4	0	0
Normal 4 - > 10	30	33.7
Increased ≥ 10	59	66.3
Platelets (thousand/mm3)	**340.7 ± 129.4 G/L**	
Decreased < 100	2	2.2
Normal ≥ 100	87	97.8
Hemoglobin (g/l)	**101.9 ± 14.5 g/L**	
Normal ≥ 110	25	28.1
Mild anemia 90 -<110	50	56.2
Moderate 60 – 90	13	14.6
Severe < 60	1	1.1

Comments: 66.3% of patients had leukocytosis, no patient had leukopenia. 2 patients (2.2%) had thrombocytopenia; Anemia accounted for 71.9%, moderate anemia was 14.6%, severe anemia was 1.1%.

Table 3. Some tests at the time of diagnosis

Indicators	n	%
ALT (U/L) (n=89)		
≥ 80 -<200	56	62.9
200- 400	21	23.6
> 400	12	13.5
AST (U/L) (n=89)		
≥ 80 -<200	33	37.1
200- 400	39	43.8
> 400	17	19.1
BilirubinTP (µmol/l) (n=86)		
Mean ± Standard deviation	123.8 ± 72.0	
Normal <20	9	10.5
Increased > 20	77	89.5
BilirubinTT (µmol/l) (n=86)		
Mean ± Standard deviation	69.2 ± 41.9	47.8
Normal < 8.6	7	8.1
Increased ≥ 8.6	79	91.2

Indicators	n	%
Albumin (g/l) (n=79)		
Mean ± Standard deviation	37.2 ± 3.4	20.2
Normal > 35	65	82.3
Decreased < 35	14	17.7
PT % (n=88)		
Mean ± Standard deviation	87.5 ± 18.5	
Normal 70-140%	79	89.8
Decreased < 70%	9	10.2
PCR CMV (copies/ml) (n= 89)	160,385.8 ± 925,551.7	
< 5000	23	25.8
5000 < 10.000	25	28.1
≥ 10.000	41	46.1

Comments: Transaminase increased in all patients, usually increased <400 U/L. Direct hyperbilirubinemia was most common (91.2%). 17.7% of patients had hypoalbuminemia; 10.2% of patients had hypoprothrombinemia. High viral load in the blood of patients was mainly ≥ 10,000 copies/ml, accounting for 46.1%.

3.3.1. General treatment results

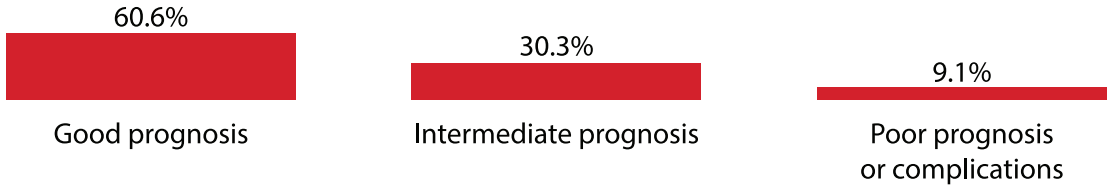

Chart 2. General Treatment Results

Comments: The rate of patients achieving treatment efficacy (good and average prognosis) is 90.9%. The prognosis group is good (60.6%), the prognosis group is medium (30.3%), and the prognosis group is poor, or with complications (9.1%).

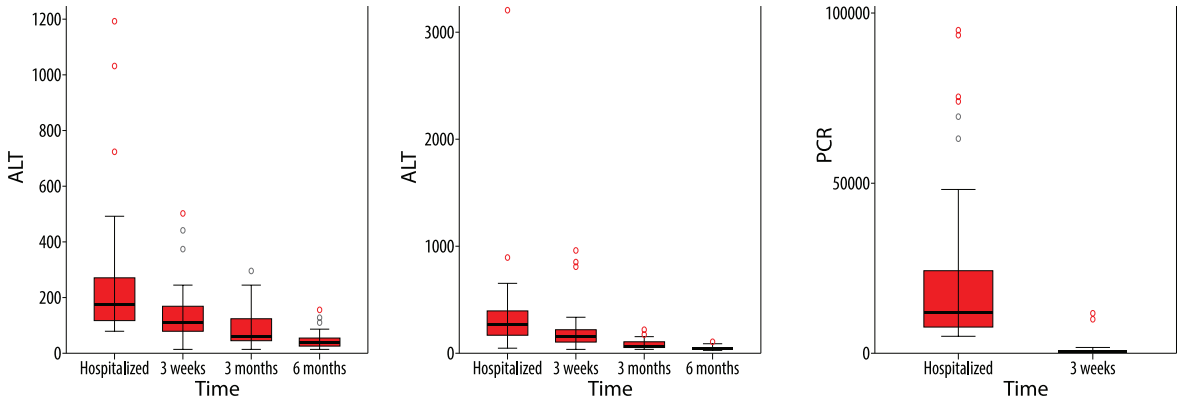

Chart 3. Characteristics of changes in transaminase and serum viral load

Comments: Transaminase index and serum viral load both decreased significantly after treatment and normalized significantly quickly, especially ALT, AST at 3 weeks.

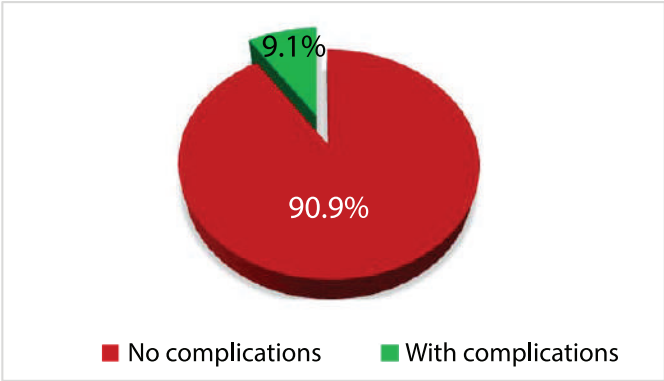

Chart 4. Post-treatment follow-up

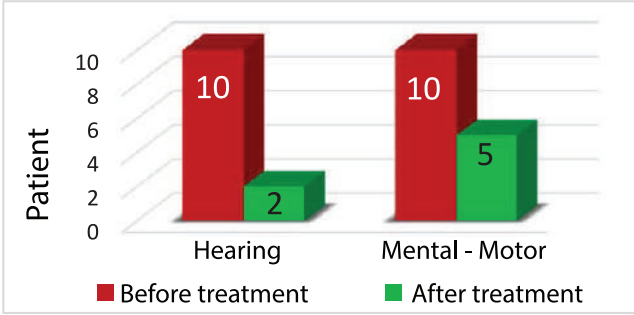

Chart 5. Hearing and mental - motor assessment after 6 months of treatment

Comments: The majority of patients had no complications of the disease during treatment (90.9%). The rate of complications after 6 months of treatment was 9.1%. No patient in the study group developed chronic liver disease or cirrhosis. Before treatment, 10 patients had hearing loss. After treatment, 1 patient had hearing loss but had significant improvement. 1 patient with hearing loss had a cochlear implant. Before treatment, 10 patients had mental and motor development delays compared to their age.

After treatment, 5 patients had improvement in mental - motor development, 5 patients had no improvement in symptoms. There were no additional patients with hearing loss and mental - motor developmental delay in the group that did not have these symptoms before. The difference was statistically significant with $p<0.001$.

IV. DISCUSSION

The study recorded 89 patients who met the criteria for disease selection and were followed for 6 months. The results showed that CMV hepatitis is common in children 1-12 months old, especially children 1-3 months old, the male/female ratio = 2.5/1, the rate of full-term and full-weight children was quite high (81.8% and 79.5% respectively), vaginal delivery (56.8%), breastfeeding was 41.6%. This result is consistent with other domestic studies [3],[4].

4.1. Clinical features

The most common symptom is jaundice (86.5%), followed by hepatomegaly (64%), feces of silver color (52.8%), subcutaneous hemorrhage (4.5%), and other associated diseases such as congenital heart disease, renal pelvis dilatation, etc. which account for 11.4%. Our study shows that CMV hepatitis is often accompanied by cholestasis in children, consistent with medical literature and other studies [4], [5].

4.2. Subclinical features

Transaminases are increased in all patients, transaminases are often slightly increased and

rarely exceed 400U/L. Direct hyperbilirubinemia was 91.2%, anemia was 71.9%, and thrombocytopenia was 2.2%. Most children do not have coagulation disorders. The results are consistent with other studies [6]. The viral load in the blood of patients is mainly ≥ 10,000 copies/ml of blood, accounting for 46.1% [5]. Our study showed a difference in CMV viral load between the 2 groups with $p < 0.05$.

4.3. Treatment results

Follow-up treatment for 6 months: 90.9% improved hepatitis. The rate of the high-average prognosis group was 30.3%. Because this is a systemic disease, the progression and effects of CMV on the patient's body take place over a long period of time; 9.1% of patients have a poor prognosis or complications. Our study results are higher than those of Celikel E, Puspita G, respectively, 59% and 68.3% [7]. Transaminase and serum viral load both decreased significantly after treatment and normalized significantly, especially at 3 weeks. Our study corresponds to the world's study and demonstrates the effectiveness of antiviral drugs in improving Transaminase and serum viral load caused by Cytomegalovirus.

Post-treatment follow-up: the majority of patients had no complications during treatment (90.9%). The rate of complications after 6 months of treatment was 9.1%. There were 5/6 patients with mental - motor developmental delay, 1/6 patients with bilateral cataracts, 2/6 patients with varying degrees of hearing loss and no patients with cirrhosis. Our study is similar to the world's study, CMV complications are not rare [8]. There was a difference in hearing and mental - motor improvement in children using antiviral drugs with $p < 0.001$. Our study is similar to the study by Lackner and Oliver 2009 [9]. This suggests that treatment of CMV infection with ganciclovir/valganciclovir has beneficially improved both hearing and neurological outcomes.

In our study, treatment of CMV hepatitis was indicated when AST, ALT > 80 IU/L, CMV PCR ≥ 5000 copies/ml and IgM-CMV antibody (+) [10]. The most common antiviral drugs for CMV treatment are intravenous ganciclovir and oral valganciclovir for 3 weeks. All of our patients treated with ganciclovir/valganciclovir showed significant recovery compared to those who did not use antiviral drugs. However, due to the short study period, we could not fully evaluate the patients' ganciclovir resistance. In addition, we did not record reactivation or recurrence of CMV hepatitis in any of our patients during the 6-month follow-up. It is noteworthy that all our patients were immunocompetent children, and this result will contribute to the limited knowledge on this topic in immunocompetent children.

V. CONCLUSIONS

CMV infection should be one of the first factors to be considered in cases of acute, persistent or chronic hepatitis, especially in young patients 1-12 months of age and early presentation. Longer study periods and further studies with larger case series of treatments in this indication are needed. Until the specific indications for ganciclovir in the treatment of CMV hepatitis in children are clearly established, each patient should be evaluated individually and adverse effects should be taken into account in the decision-making process.

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