

CLINICAL ASPECTS IN EPSTEIN-BARR AND CYTOMEGALIC VIRUS CO-INFECTION IN CHILDREN

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Abstract

Background - Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) usually cause primary and latent infections during childhood. Thus, a co-infection with these viruses can also occur occasionally in children. However, its clinical impact has not been yet established, and may be underestimated.

Aim – The authors described 5 cases of Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) co-infection in children, emphasizing the polymorphism of clinical manifestations.

Methods - Case report 1 is a 3 years old child with prolonged fever in the context of a good general condition. Case report 2 is a 18-month-old toddler with hepatocytolysis and mild jaundice. Case report 3 is a 5 years old child with acute tonsillitis and generalized adenomegaly. Case report 4 is a teenager with toxic appearance, prolonged high fevers, chills, fatigue, and malaise, myalgias, headache, and pain in the left upper quadrant, splenomegaly. Case 5 is a teenager with high fever, myalgias, headache, acute tonsillitis, hepatosplenomegaly, exudative pharyngitis and cervical lymphadenopathy, moderately elevated serum levels of aminotransferases. In all cases the serology was positive for EBV and CMV.

Conclusions - The authors noticed the atypical expression of the 2 viruses in young age and the presence of classical elements of mononucleosis in a wide range and severe expression in adolescents.

Key words: Epstein Barr and cytomegalic virus, clinical aspects, child

Introduction

Infectious mononucleosis (IM) is a clinical syndrome most common among adolescents and young adults. It is characterised by fever, pharyngitis, fatigue, lymphadenopathy and hepatosplenomegaly. This viral disease is caused mainly by the Epstein-Barr (EBV) virus and Cytomegalovirus (CMV). These viruses can lie dormant and could be reactivated under host immunosuppression conditions or by stimulation by other germs. However, most

of the time there is a multiple etiology of the disease. This involves associations between viruses, the most frequent being between the Epstein-Barr virus (EBV) and Cytomegalovirus (CMV).

The diagnostic of IM can be done using serological tests that look for specific antibodies associated with the viruses such as capsid antigen (VCA) antibodies- IgM ± capsid antigen (VCA)-IgG, nuclear antigen (EBNA)-IgG, of anti-CMV antibodies-IgM, anti-CMV antibodies-IgG.

The search for these antibodies is a means of defining infection status as shown below or for differential diagnostic as the mononucleosis syndrome can be caused by other pathogens.

The acute infection with EBV is indicated by the presence of capsid antigen (VCA) antibodies- IgM ± capsid antigen (VCA)-IgG and the chronic infection is defined by the presence of nuclear antigen (EBNA)-IgG.

The acute infection with CMV is indicated by the presence of anti-CMV antibodies-IgM and the chronic infection by the anti-CMV antibodies-IgG.

The co-infection involves association of capsid antigen (VCA-IgM) ± capsid antigen (VCA-IgG) + anti CMV-IgM (1,2,3). This double infection can occur simultaneously or after a short time interval (IgM persist between 1 week and 3 months).

There is a possibility to reactivate these dormant viruses → EBV determine a decrease of the immunity with the decrease of the CD₄/CD₈ ratio and the possibility of expressing the latent infection with CMV (3,5,6).

Although is considered that the infections with CMV and EBV are more frequent in adolescents, it seems that the primary infection occurs at a younger age, the expression of the mononucleosis syndrome being more attenuated (4,7,9).

Beside IM, EBV is also involved in the Kawasaki disease, anaphylactoid purpura, immune thrombocytopenic purpura, juvenile rheumatoid arthritis.

The clinical manifestations of IM include: high or prolonged fever, pharyngitis, lymphadenopathy, hard palate petechiae, rash, hepatosplenomegaly.

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The aim of this work

The aim of the present study is to outline the main clinical elements of the EBV + CMV co-infection in children.

Materials and method

Description of the clinical particularities in 5 children aged between 1 year and 8 months and 17 years diagnosed in the specialized ambulatory with a CMV – EBV co-infection (positive VCA-IgM, positive CMV-IgM and negative EBNA – IgG).

CASE 1

NA, 3 years old male, having for 10 days persistent fever with spikes at fixed hours (9⁰⁰, 18⁰⁰) amid an unchanged general state. Ten days after the first spike in fever, at the physical examination, an intensely congested larynx is noted with pultaceous deposits, lateral cervical adenopathy, without complaints.

The atypical picture, prolonged evolution, the erithemato-pultaceous aspect of the angina at this young age and the generally good state has raised the suspicion of a IM.

Biologically, leukocytosis and monocytosis were detected and, the double infection with EBV and CMV was confirmed serologically.

CASE 2

CN, 1 year and 6 months old male, 6 days from the onset with fever with loss of appetite

Clinical aspect: discrete subicteric sclera

Biology: hepatic cytolysis (230 – 200 U/l), slightly increased direct bilirubin

The expanded range of investigations for the hepatic ailment detected the presence of positive IgM for CMV and EBV.

CASE 3

MA, 5 years old male, showing for 3 days high fever, dysphagia and adeno pharyngitis

Clinical aspect: enlarged tonsils, pseudomembranous deposits, lateral cervical adenopathy with swollen lymph nodes that are partially adherent, mobile and sensitive without signs of acute inflammation and with a proconsular neck aspect.

Biology: leukocytosis, lymphomonocytosis

Serology: confirmation of the co-infection

CASE 4

CA, 17 years old male.

Onset 2-3 days with high fever, affected general state, pain, marked fatigue, myalgia, headache, and left upper quadrant pain.

Clinical aspect: adenopathy, splenomegaly (explaining the constant left upper quadrant pain).

Stage diagnostic: food poisoning, flu

Abdominal echography: hepatosplenomegaly

Biology: leukocytosis, lymphomonocytosis, IgM CMV + EB, discrete hepatic cytolysis 200 UI/l.

CASE 5

RA, 15 years old female

Shows for 5 days high fever, headache, dysphagia

Clinical aspect: tonsils with pseudomembranous deposits, hepatosplenomegaly, lateral cervical adenopathy

Biology: mononucleosis syndrome – etiology confirmed by positive IgM for EBV and CMV.

Results and discussion

The clinical expressions of each individual case are shown in Table 1.

Table 1. Mononucleosis syndrome – main characteristics.

Main characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
General state	good	good	moderately affected	affected	affected
Adenomegaly	+	-	+++ (proconsular neck)	-	++
Pharyngitis	+ erithemato-pultaceous	-	+ pseudo-membrane	pultaceous	+ pseudo-membrane
Hepatomegaly	-	+	-	+	+
Splenomegaly	-	-	-	+ Left upper quadrant pain	+
Rash	-	-	-	-	-
Jaundice	-	±	-	-	-
Fatigue	-	-	-	+	+
Myalgia	-	?	-	+	+
Headache	?	?	-	+	+
Leukocytosis	+	+	+	+	-
Lymphomonocytosis	+	+	+	+	+
R. hepatic	-	+	-	+	+

It can be observed that as the child grows, the mononucleosis picture is more complex, including more elements.

In adolescents, the co-infection accentuates the IM picture that is expressed by fever, angina, adenohepatosplenomegaly amid an affected state, sometimes with flu like symptoms (head ache, fatigue, myalgia).

At young ages, atypical or subtle forms are predominant (prolonged febrile syndrome, loss of appetite and well tolerated erythematous tonsillitis).

None of the above cases has shown a rash or eyelid edema that were previously reported in literature (3, 5, 6, 8, 9, 10).

Ito (2009) described 3 cases in 1-3 years old children with EBV and CMV co-infection with IM, acute hepatitis and hemophagocytic lymphohistiocytosis with extended evolution (7).

Wang (2009) in a study on 190 patients with IM has identified 7 subjects with EBV and CMV co-infection of which 6 were younger than 6 years. All presented the typical signs on IM (fever, pharyngitis lymphadenopathy, petechiae). Furthermore, only four had also had hepatosplenomegaly and none of them had rashes (13).

These observations are overlapping with the ones from our study, on young children (fever, tonsillitis, good general state → as mode of expression).

Chan's study (2003) on 77 children with IM has shown a peak of the co-infection between 2-4 years expressed by fever, pharyngitis, lymphadenopathy. The hepatic affections occur in older children.

Studies done by Zenda (2004) (14) and Bravender (2010) (1) confirm that in adolescents the picture respects the clinical elements, also associating the hepatosplenomegaly, liver cirrhosis elements, headaches and myalgias. These observations are similar with the observations made on the adolescents from the present study.

According to Olson D., and Huntington MK. (2009) the latent infection with EBV is reactivated by the CMV acute infection. Nishikawa J. Et al. (2011) (11) consider that the acute infection with EBV can trigger a cross-reactance reaction with the synthesis of anti M protein antibodies of other herpes viruses. Guerrero-Ramos A et al.(2015) (12) have verified the efficiency of the Architect EBV panel in isolated infections or EBV-CMV co-infections. Testing for CMV is strongly recommended for the interpretation of a EBV infection model.

Conclusions

1. CMV + EBV co-infection has different expression depending on the age of the pediatric patients.
2. Young age associates the subtle elements (fever, tonsillitis) amid a satisfactory general state
3. The adolescence shows an intense mononucleosis syndrome with complex clinical elements and severity stages. Hepatitis occurs mainly in this situation.
4. In atypical, subtle or severe IM forms there is probably a multiple etiology.
5. There is a suspicion of a reciprocal latent activation by an active infection both for EBV and CMV. Therefore this aspect needs further investigation.

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