# Neonatal gastrointestinal involvement and congenital cytomegalovirus

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## Abstract

Cytomegalovirus (CMV) is the most common cause of congenital viral infection, affecting 0.2 to 2.3% of all live births in developed countries. Very low birth weight and extremely low birth weight newborns are at higher risk of symptomatic CMV infection, most commonly secondary and acquired through breast milk. Gastrointestinal involvement is rare in acquired CMV infections, but it could be an important manifestation of postnatal infection in preterm infants admitted to neonatal intensive care units. Early onset of CMV gastrointestinal signs/symptoms is very rare. In a review of the literature it is described in 5 newborns in the first 24 hours of life, and 6 considering the onset in the first week of life. This review describes also a case report of congenital CMV in an immunocompetent newborn with onset of gastrointestinal signs immediately after birth: a possible association between viral infection and enteric manifestations was considered in the differential diagnosis. A review of the literature of the different case reports found has done, with description and comparison of the different patients and clinical presentations.

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Key words: Cytomegalovirus; Congenital viral infection; Gastrointestinal involvement; Neonate.

Conflict of interest: the authors declare no potential conflict of interest.

Contributions: AP looked after the patient described in the case report during admission, reviewed the literature about congenital/postnatal cytomegalovirus and gastrointestinal involvement, drafted the manuscript and approved the final manuscript as submitted. AA, MB, RMC, and SF looked after the patient described in the case report during admission, reviewed and revised the manuscript, and approved the final manuscript as submitted. SM and LP are the heads of the two departments where the patient was admitted. They looked after the patient described in the case report during admission, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Received for publication: 12 March 2016.
Revision received: 22 June 2016.
Accepted for publication: 19 July 2016.


*La Pediatria Medica e Chirurgica 2016; 38:134*
*doi:10.4081/pmc.2016.134*

## Introduction

Cytomegalovirus (CMV) is the most common cause of congenital viral infection, affecting 0.2 to 2.3% of all live births in developed countries;[1-12] it is also estimated as the leading infectious cause of non-genetic hearing loss, mental retardation[1,2,13-15] and non-genetic congenital malformations.[16] Very low birth weight and extremely low birth weight newborns are at higher risk of symptomatic CMV infection, most commonly secondary, acquired through breast milk.[17]

Maternal primary CMV infection or reinfection during pregnancy are the cause of neonatal congenital infection, with a mean risk of transmission of 40% (24-75%),[3,18] lower in the first three months (36%) than in the last three months of gestation (78%).[3,19]

Considering all the infected newborns, only 5 to 10% are symptomatic at birth, in particular with neurodevelopmental delay signs and sensorial hearing loss. Among asymptomatic patients, 10% to 15% will show developmental disorders, mainly sensory hearing loss.[1,2,8,10,11,13,14,20-22] Most of congenital infections (85-90%) remain asymptomatic:[3,16,23] among them, 8 to 15% will show developmental disorders or sensorial hearing loss.[1-3,13,14]

Possible signs and symptoms of congenital CMV infection with onset at birth are the following:[3,16,24] unilateral or bilateral sensorial hearing loss, visual loss, microcephaly, hepatomegaly and/or hepatitis, splenomegaly, thrombocytopenia, jaundice, petechiae, motor defects, mental disability, chorioretinitis, strabismus, optic atrophy, dental defects. Rarely it could present as a severe multi organ dysfunction with polyserositis.

Gastrointestinal involvement is considered very rare in congenital and acquired CMV infection.[7,8,10,11,20] On the other hand, CMV gastrointestinal symptoms could be an important manifestation of postnatal infection in patients admitted to neonatal intensive care units[25] or a manifestation of CMV intestinal disease in immunocompromised patients or patients affected by inflammatory bowel disease.[22,26-33] A rare presentation with intestinal polyps in immunocompetent healthy patients has also been described.[34]

## Case Report

A 2330-g female was born at 37 weeks of gestational age through urgent cesarean delivery, necessary due to alterations in foetal cardiac pulse, decline of growth and ultrasound finding of abnormal bowel distension. During pregnancy, serologic conversion for CMV was docu-

mented in the third trimester. APGAR score was 2 after the first minute, and 7 at the 5th minute of life.

Due to an important abdominal distension observed immediately after birth, an underlying abdominal pathology was suspected: the patient was promptly transferred to a third level neonatal centre, the neonatal intensive care unit of Niguarda Hospital (Milan, Italy).

Since birth, the baby had passed liquid meconium with subsequent mucus and liquid stools. Radiologic examinations performed immediately after admission showed small-intestinal distension with a widespread intestinal wall thickening. Through thoracic and abdominal X-ray, abdominal ultrasound and neonatal-surgery expert advice, surgical pathologies were excluded.

Oral feeding was started on the 3rd day of life, with good tolerance but persistence of liquid stools, suggesting colitis as cause of the symptoms.

Urine and blood were tested for CMV DNA through polymerase chain reaction, yielding positive results (1.296.341 and 2.322 copies/mL, respectively). All the other examinations carried out to exclude other CMV localizations (ophthalmologic examination, brain ultrasound) were normal. No specific analysis to confirm a possible relation between CMV and enteric symptoms, such as intestinal biopsy, were done, due to the rapid and progressive improvement of the patient. So we hypothesized a possible association between CMV and gastrointestinal involvement, but it was not proven with invasive tests.

On the 7th day of life, the patient was transferred back to our unit. During hospital stay, gastrointestinal symptoms progressively improved until normalization, with good oral feeding tolerance of both maternal and formula milk and a very good growth curve. Moreover, brain and abdominal ultrasonographies were normal. A follow-up brain magnetic resonance was negative. Neurologic development was normal, with a physiologic course. Any antiviral treatment was started.

## Discussion

Congenital CMV is currently considered the most common congenital viral infection, with a prevalence of 0.2% to 2.3% in developed countries[1-12] and 0.57 to 1% in Italy.[3,35]

Even though gastrointestinal involvement due to congenital or immediately post-natal CMV infection has been considered extremely rare, some case reports have been found in the literature. Table 1 summarizes all the case reports and articles found in a review of the liter-



**Table 1. Review of the literature: case reports of congenital or postnatal cytomegalovirus infection and gastrointestinal involvement with onset within 90 days of life.**

| Article details: author, year (city, country) | Issues |
|---|---|
| Gretillat *et al*., 1979 (France)[36] | CMV inclusions in the intestine of an infant with NEC |
| Sann *et al.,* 1981 (France)[37] | Of 11 newborns with NEC, 7 of them had CMV infection. NEC accounted for 22% of all clinical manifestations of CMV infection |
| Hershlag *et al*., 1984 (Jerusalem, Israel)[38] | CMV infection in a patient with Hirschsprung's disease |
| D'agostino *et al*., 1988 (Vicenza, Italy)[39] | Histologic finding of CMV infection in a post-NEC stenosis |
| Fournier *et al*., 1989 (Lyon-Sud, France)[40] | CMV cells in a preterm newborn with NEC and colonic stenosis. Onset: 28th day of life |
| Déchelotte *et al*., 1992 (Clemont Ferrand, France)[41] | Three cases of ileal involvement due to CMV infection of foetus and placenta, two of which with ultrasonography abnormalities of the foetal lower abdomen, and all with CMV inclusions in intestinal samples |
| Huang *et al*., 1996 (Taoyuna, Taiwan)[11] | Ileal perforation in term newborn with congenital or perinatal CMV. Birth weight 3500 g, onset at 42nd day of life |
| Jonkhoff-Slok *et al*., 1997 (Haarlem, The Netherlands)[42] | Diarrhoea and rectal bleeding in a 5-week-old infant with CMV colitis. Born at term |
| Hakim *et al*., 1997 (Brooklyn, NY, USA)[43] | Congenital CMV and viral inclusions in ileal ulceration (36 WGA newborn, onset at birth) |
| Reyes *et al*., 1997 (Orange, CA, USA)[22] | CMV enteritis in a preterm newborn (33 weeks of gestational age, birth weight 2200 g). Onset at 5th weeks of age |
| Stiskal *et al*., 1997 (New Brunswick, NJ, USA)[44] | Congenital CMV infection with gastrointestinal involvement (necrotizing enterocolitis) in a 34 WGA, birth weight 2695 g, onset at 31st day of life |
| Fox *et al*., 1999 (Farmington, CT, USA)[45] | Fever and intractable diarrohea in a 5 weeks old infant due to CMV-induced enterocolitis. Born at term |
| Quiros-Tejeira *et al*., 1999 (Los Angeles, CA, USA)[46] | CMV enterocolitis in an infant, born at term, onset at 60 days of life |
| Asabe *et al*., 2003 (Fukuoka, Japan)[20] | Pseudo-Hirschsprung's disease and congenital CMV in a term newborn, birth weight 1952 g, with onset immediately after delivery |
| Hinds *et al*., 2004 (London, UK)[47] | Bloody diarrhoea due to CMV colitis in a 2-month-old immunocompetent child |
| Rongkavilit *et al*., 2004 (Detroit, MI, USA)[48] | Severe CMV enterocolitis in an immunocompetent infant, birth at term, onset at 60th day of life |
| Gessler *et al*., 2004 (Zurich, Switzerland)[49] | Postnatal CMV infection and CMV-associated enterocolitis in a 29 WGA newborn, onset at 6th day of life, birth weight 1490 g |
| Cheong *et al*., 2004 (London, UK)[25] | Description of 11 infants with postnatal CMV infection and gastrointestinal manifestations observed in a 5-year period |
| Ekema *et al*., 2006 (Brescia, Italy)[5] | Colonic stricture mimicking Hirschsprung's disease and congenital CMV in 37 WGA newborn, birth weight 2490 g. Onset at 34th day of life |

**To be continued on next page**

ature. Using PubMed and OVID MEDLINE®, the following key words were searched in titles and abstracts: cytomegalovirus AND colitis or intestine or intestinal or bowel or colic or Hirschsprung AND infant or neonatal or neonate or newborn. Only reports regarding newborns and infants under 3 months of age were considered.

Thirty-eight articles were found up to July 2015. The first report dates back to 1979, when Gretillat *et al*.[36] described a correlation between necrotizing enterocolitis (NEC) and CMV infection, based on inclusion bodies on pathologic examination of bowel specimens.

Most of the studies revealed a possible association between CMV infection and enteritis,[22,37,38] enterocolitis,[25,42,45-51,54-56,59-61,64] and NEC,[17,25,33,36,37,39,40,44,63,65] often with finding of CMV inclusions in histological intestinal samples. It is debatable whether the virus has a role in the pathogenesis of the diseases, either directly or as a secondary super-infection after the acute phase of the enterocolitis.[5,22,39,40,53]

Two articles[20,38] reported a possible connection between congenital CMV and Hirschsprung's or pseudo-Hirschsprung's disease.

Four other reports[11,38,50,51] described a possible association between CMV infection and intestinal perforation: two ileal perforations,[11,43] one perforated appendicitis as a complication of CMV enterocolitis[51] and one Merkel's diverticulum perforation.[50]

Déchelotte *et al*.[41] described 3 cases of pseudo-meconium ileus caused by a CMV infection, two of which with antenatal ultrasound detection of increased echogenicity of the lower foetal abdomen.

In a 5 year period, Cheong *et al*.,[25] in the neonatal intensive care units of Queen Charlotte's and Chelsea and Hammersmith Hospitals, identified 16 infants with postnatal CMV infection, eleven of whom with gastrointestinal signs.

Bonnard *et al*.,[50] in a 5-year retrospective study involving neonates operated for gastrointestinal conditions, described the presence of CMV inclusions in five cases: two NEC, two complications of Meckel's diverticulum (volvulus and perforation) and one distal ileal atresia.

A possible correlation between primary colonic stricture and CMV infection was described in three case reports,[5,52,57] whereas two articles[53,66] reported an association between ileal stricture and CMV enteritis. Post-necrotizing enterocolitis strictures have been described in three reports.[39,40,65] Hendriks *et al*.[62] described an association between CMV infection and intestinal obstruction without strictures.

When data was available, the onset of gastrointestinal symptoms in the first 24 hours of life[20,43,50,62] or in the first 7 days of life[49] was rarely reported and, respectively, in patients with: ileal ulceration,[43] pseudo-

**Table 1. Continued from previous page.**

| Article details: author, year (city, country) | Issues |
|---|---|
| Bonnard *et al*., 2006 (Paris, France)[50] | CMV infections described in 5 neonates operated for gastrointestinal conditions (2 enterocolitis, 2 complications of Merkel's diverticulum, 1 distal ileal atresia). Average WGA 34+4 weeks, average birth weight 2364 g. Onset at 1 to 51 days of life |
| Terry *et al*., 2006 (Savannah Campus, USA)[51] | CMV enterocolitis complicated by perforated appendicitis in a premature infant (30 WGA, onset at 9 weeks of age) |
| Shetty *et al*., 2007 (Cardiff, UK)[52] | CMV as cause of colonic stricture in a premature infant (27+2 WGA, birth weight 490 g, onset at 36th days of life) |
| Srinivasjois *et al*., 2008 (Perth, Australia)[53] | CMV-associated enteritis and ileal stricture in a 23+5 WGA preterm newborn, birth weight 580 g, onset at 90th day of life |
| Abdulhannan *et al*., 2008 (Leeds, UK)[54] | Primary CMV colitis in a 74 days old infant, born at term |
| Nigro *et al*., 2010 (L'Aquila, Italy)[55] | Description of three infants with prenatal or immediately postnatal CMV infection with severe enterocolitis (onset 1-3 months of life) |
| Fischer *et al*., 2010 (Lausanne, Switzerland)[56] | Acquired postnatal CMV infection in an extremely low birth weight infant, that presented with colitis in a multi-organ syndrome |
| Tzialla *et al*., 2010 (Pavia, Italy)[57] | Large bowel stricture and retinitis due to CMV in an immunocompetent infant, onset at 20th day of life. Born at 37 WGA, birth weight 2490 g |
| Berardi *et al*., 2011 (Modena, Italy)[58] | Acquired CMV colitis and anaemia in a 2 months old infant with previous surgery for ileum-caecal valve atresia. Born at term, birth weight 3255 g |
| Irizarry *et al*. 2011 (Tampa, FL, USA)[59] | Congenitally infected infant with primary CMV enterocolitis, successfully treated with oral valgancyclovir |
| Bar-Meir *et al*., 2012 (Chicago, IL, USA)[33] | CMV NEC in 26 WGA premature infant, birth weight, 864 g. Onset: 29th day of life |
| Refai *et al*., 2012 (Brighton, UK)[60] | CMV enterocolitis acquired in the 5th week of life in a term newborn (birth weight 3700 g) |
| Lee *et al*. 2012 (Los Angeles, CA, USA)[61] | CMV enterocolitis in a premature newborn (27+4 WGA, birth weight 1130 g, onset at 34th day of life) |
| Unl soy Aksu *et al*. 2013 (Ankara, Turkey)[53] | Description of CMV enteritis and jejunal stricture in a preterm infant Hendriks *et al*., 2013 (Liverpool, UK)[62] Term newborn, birth weight 3680 g, with perinatal CMV infection, bilious vomiting and abdominal distensions. Onset at 12 h of life |
| Tengsupakul *et al*., 2013 (Minneapolis, MN, USA)[17] | Postnatal acquired CMV with septic syndrome and NEC in a 24+5 WGA preterm infant, birth weight 800 g, onset in the 5th week of life |
| Tran *et al*., 2013 (Baton Rouge, LA, USA)[63] | NEC and CMV in a premature infant (25+1 WGA, birth weight 653 g). Onset at 48th day of life but history of feeding difficulties after the first week of life |
| Louazon *et al*., 2014 (Bron Cedex, France)[64] | CMV enterocolitis, onset at 10 weeks of age. Term infant, birt weight 3150 g |
| Marseglia *et al*., 2015 (Messina, Italy)[65] | Acquired CMV infection in a term newborn with NEC and consequent colonic stenosis. Birth weight 2780 g, onset at 8th day of life |

CMV, cytomegalovirus; NEC, necrotizing enterocolitis; WGA, weeks for gestational age.

Hirschsprung's disease,[20] Merkel's diverticulum perforation,[50] ileal atresia,[50] intestinal obstruction[62] and enterocolitis.[49]

The review of the literature suggests that is important to suspect CMV as possible etiologic cause of gastrointestinal symptoms with unknown origin in newborns. The diagnosis of congenital CMV can be done with urine analysis for CMV DNA, a non-invasive and accurate test.

The treatment of congenital CMV infection remains an open and debatable field. While there is agreement to treat CMV positive cases with neurological involvement, and avoiding treatment of CMV positive but asymptomatic patients, the necessity to treat CMV positive newborns with non-neurologic symptoms is controversial. It's also debatable the real necessity to do the intestinal biopsy in suspected cases, since it is invasive and with uncertain utility on clinical practice.

## Conclusions

Gastrointestinal involvement during congenital and post-natal CMV infection is uncommon, in particular in immunocompetent and physiologic newborns. Particularly rare is the onset of these manifestations in the first 24 h of life. The possible association between congenital infection and gastrointestinal involvement has to be suspected in newborns with specific symptoms and unknown origin. The role of invasive tests, such as the intestinal biopsy, and the necessity of a specific antiviral treatment should be considered accurately on each single case, basing also on the review of the literature and recent scientific evaluations.

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