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Cytomegalo Virus as a Possible Risk Factor for Neonatal Gastrointestinal Surgical Conditions

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The present work aims to evaluate the possible causal relationship between CMV infection and gastrointestinal surgical conditions in the neonates. 33 neonate operated on because of gastrointestinal surgical conditions in Assiut University Children Hospital. Detection of CMV IgG and IgM from both mother and newborn was done. Surgical specimen was taken for pathologic examination. Positive serological tests (CMV IgM) were found only in four neonates (3 males and one female). Maternal CMV IgM were positive only in two cases. All surgical specimens showed characteristic CMV nuclear inclusion bodies.

Keywords cytomegalo virus, neonates, gastrointestinal surgical conditions

INTRODUCTION

Cytomegalovirus (CMV) is a member of the herpes virus group that is widely distributed. It is the most common intrauterine infection in humans, with a reported prevalence ranging from 0.2 to 2.4% with higher rates among populations of low socioeconomic state [1]. Congenital infections occur through transplacental passage of CMV during maternal viraemia. Then the virus spreads hematogenously through the fetus to reach the major target organs [2, 3]. Only 5% of children are symptomatic during the neonatal period [4–7]. The diagnosis of congenital CMV is best established by isolation of the virus within the first 2 weeks of life. Detection beyond this point may reflect perinatal acquisition [3]. Gastrointestinal (GI) inffection is considered infrequent in neonates [3, 7]. In cases of gastrointestinal tract infection, the clinical spectrum ranges from esophagitis, diarrhea, gastric hemorrhage, deep ulcers anywhere in the gastrointestinal tract to more severe surgical complications [8]. Several reports of surgical manifestations of CMV involvement in necrotizing enterocolitis (NEC), meconium peritonitis, intestinal perforation and intestinal atresia, perforation from Meckel's diverticulum, and colonic stricture have been published [3, 7, 9–13]. Therefore congenital CMV meets certain criteria for newborn screening; it is more common than general disorders included in newborn screening programs combined, and it is a leading cause of disability in children [14].

The aim of the present work is to evaluate the possible causal relationship between congenital CMV infection and gastrointestinal surgical emergencies in neonates admitted to the neonatal ICU and pediatric surgical departments of Assiut University Children's Hospital.

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TABLE 1 Demographic, clinical and laboratory data of CMV IgM positive newborn infants at presentation

Case (no)	Sex	G.A. (wks)	Type of Labor	Age of Presentation (days)	Wt (Kg)	HB (g/dL)	Pl ($\times 10^9$/l)	WBC ($\times 10^3$/ul)	Maternal Serology for CMV	Neonatal Serology for CMV
1	♂	34	Vaginal	2	2.75	16	474	15.7	IgG +, IgM−	Ig M +
2	♀	36	Cs	4	3.8	10.6	269	14.3	IgG +, Ig M +	Ig M +
3	♂	30	Vaginal	3	2.5	14.2	138	16	IgG +, Ig M +	Ig M +
4	♂	38	Vaginal	4	3	15.1	238	11.6	IgG+, Ig M−	Ig M +

Abbreviations: Hb – hemoglobin; WBC – white blood cells; Pl – platelet; G.A.- gestational age; Wt – weight
♂ – male; ♀ – female.

PATIENTS AND METHODS

This study included 33 neonates operated upon for gastrointestinal surgical emergencies in Assiut University Children's Hospital from October 2006 to April 2007. They were 18 males and 15 females, all of them presented within the first 2 weeks of life. They were 10 cases with small intestinal atresia, 10 cases with anorectal malformation, 4 cases with meconial perforations, 6 cases with obstructed congenital megacolon, and 3 cases with NEC. An informed written consent was obtained from the parents or caregiver. All studied patients were subjected to full clinical history including obstetric and prenatal history as well as thorough clinical examination. The following investigations were done to all cases: complete blood picture, liver function tests, fundus examination, and x-ray skull. Detection of serum CMV IgG and IgM in both mothers and newborns was determined by an enzyme-linked immunoabsorbent assay. The results are read by a microwell reader compared in a parallel manner with calibrator and controls. All patients were resuscitated by nasogastric suction, IV fluids, broad spectrum antibiotics, correction of electrolyte disturbances, and acid base balance. Surgical exploration was done to all patients according to their individual surgical conditions. Surgical specimens were taken from the affected part of the gastrointestinal tract of the newborn for histopathologic examination. All specimens were fixed in formaline 10%, paraffin embedded, and routinely examined by H&E stain. Multiple sections were examined from both abnormal and apparently healthy areas.

RESULTS

Positive serological tests (CMV IgM) were found only in four neonates (3 males and 1 female). The average gestational age was 34.5 weeks (range 30–38 weeks) and the average birthweight was 3 kg (range 2.5–3.8 kg). All of them showed more or less normal obstetric and prenatal history, with no history of previous blood transfusion. Two newborn infants had small intestinal atresia, one had high imperforate anus and microcephaly, and the fourth had meconial perforation. All cases had no visromegaly, sepsis, hemorrhage, or intracranial calcifications and had a normal liver function test and fundus examination. The clinical, laboratory, and serological data of these patients are shown in Table 1. The surgical data are shown in Table 2.

Each of the four newborns showed a smooth post-operative period and received a ganciclovir 6 mg/kg/ dose every 12 h for 6 weeks.

TABLE 2 Diagnosis, surgical management and pathological findings of CMV IgM positive newborn infants

Case (no.)	Diagnosis	Surgical Management	Pathologic Findings
1	High imperforate anus and microcephaly	Colostomy	CMV inclusion
2	Small intestinal atresia (Type III a atresia)	Resection anastomosis	CMV inclusion
3	Meconial perforation (Dilated small intestinal loops and dense adhesions)	Abdominal exploration and Bishop-Koop stoma	CMV inclusion Ulceration, vasculitis
4	Small intestinal atresia (Type III intestinal atresia)	Resection anastomosis	CMV inclusion

Characteristic CMV nuclear inclusion was detected in the surgical specimens obtained from all four newborns. The surgical specimens showed a large cell containing characteristic intranuclear inclusion, which is sometimes surrounded by a clear halo ("owl's eye" effect) and is frequently associated with clusters of intracytoplasmic inclusions. Cytomegalic cells showed an infection of various cell types including vascular endothelium, fibroblasts, and smooth muscle cells and epithelial cells and associated sometimes with vasculitis. Some cells showed a lack of halo around the inclusion (Figure 1).

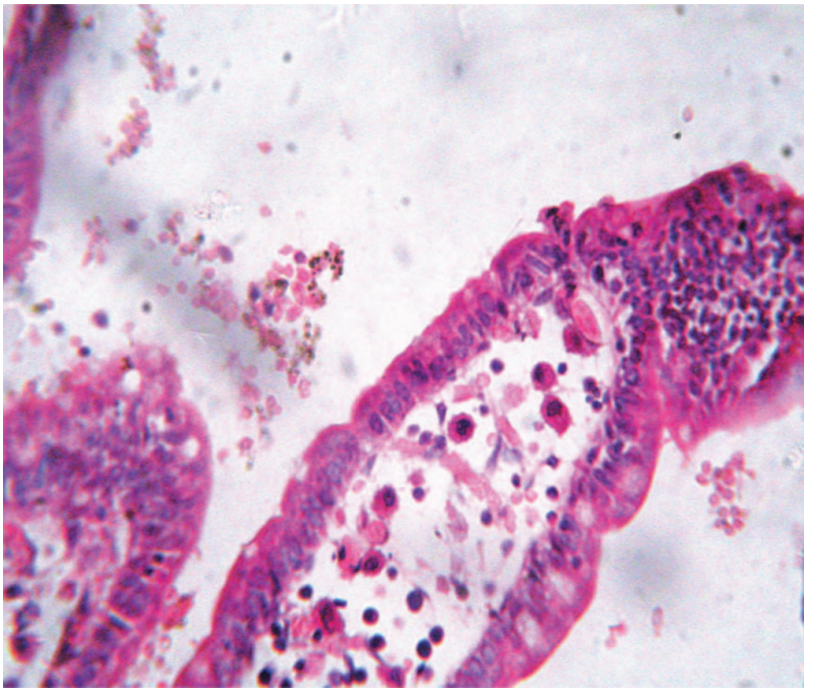

FIGURE 1 CMV infection with cytomegaly and an intranuclear inclusion (H&E stain, original magnification ×400).

DISCUSSION

Cytomegalovirus commonly infects people across the spectrum of all ages, races, ethnic groups, and those from a variety of socio-economic, cultural, and geographic backgrounds. Although most CMV infections are asymptomatic or cause mild disease, the virus can cause serious disease in newborns and immuno-compromised children [15]. Out of 33 newborn infants included in this study, we report a series of 4 neonates with gastrointestinal surgical emergencies who were seropositive for CMV IgM and all had the characteristic Cytomegalovirus nuclear inclusions in their surgical specimens. Our figure is higher than that reported by previous authers [13]. This difference may be due to the difference in geographic regions and the socio-economic status of the patients in different studies. It is well known that in developing countries the population with low economic resources usually have a high seroprevalence for CMV than those in developed countries [15–17]. Hospital-based screening of infants for congenital CMV through the use of cultured urine specimens has been conducted in the past by several U.S. academic medical center hospitals [18, 19]. Laboratory testing of urine specimens collected from newborn infants suspected of having congenital CMV is often conducted as part of clinical practice, although not consistently [14]. The best diagnostic test for establishing CMV infection is CMV IgM antibodies, which should be positive in the majority of patients during the symptomatic phase of illness. However, antibodies may not peak until 4 to 7 weeks after infection and may remain elevated up to 1 year or longer following acute infection [20]. Because all four newborn infants were positive for CMV IgM, in the first 2 weeks of life, this indicates that CMV infection may be related to intrauterine infection (congenital CMV infection). The intrauterine transmission and adverse outcome are mainly related to primary maternal infection [13]. However, the presence of maternal antibodies does not completely prevent transmission of CMV to the fetus, but reduces transmission and its adverse effects [3]. In our series, positive serologic tests (CMV IgM) were found in all four neonates, where all their mothers had positive IgG, but only two of them had positive IgM for CMV. In 2003, Taylor [20] reported that the level of IgG antibodies against CMV increases at least four-fold during acute infection and this may explain the difference between neonatal four cases and maternal two cases positive for (CMV IgM). Histologically, the detection of the distinct "owl's eye" inclusion bodies on tissue sample can be a highly specific method for determining organ involvement of CMV [21]. In the present work, the characteristic CMV nuclear inclusion was detected in the surgical specimens from the four newborns. This supports the possibility of involvement of CMV in these surgical conditions. However, there is yet no evidence that CMV can be a primary or a single cause of these manifestations. The prevalence of asymptomatic infection and the opportunistic nature of the virus make coincidental association common [11–13]. Although many GI cell types may be infected by CMV, the vascular endothelial cell is the most common [22]. According to Kosloske et al. [10], the intestinal atresia may have been related to intrauterine vasculitis of the developing midgut. The diagnosis of vasculitis is made when there is clearly abnormal vessel architecture with necrosis and characteristic viral inclusions in the involved endothelial cells [23].

Only one of our patients had microcephaly and the other three newborns did not show other features of congenital CMV infection. The absence of these features does not rule out congenital CMV infection as infants born to mothers with CMV infection are rarely symptomatic at birth [5, 24]. Only 5% of all congenitally infected infants have severe disease, 5% have mild involvement, and 90% have subclinical or chronic CMV infection [5]. Even if asymptomatic at birth, approximately 5 to 17% will have neurodevelopmental abnormalities, including sensorineural hearing loss, which may only become apparent in infancy or later in childhood. Continuous follow-up of those

neonates is recommended till the preschool age [3, 25]. Treatment of congenital CMV infection with ganciclovir (6 mg/kg dose every 12 h for the first 6 weeks of life) not only prevents hearing deterioration but also improves or maintains normal hearing function even in asymptomatic infant [26, 27]. All four neonates included in this study who had positive IgM for CMV and characteristic CMV nuclear inclusion in their surgical specimens received ganciclovir for 6 weeks. Although it is a major health problem, serologic and virologic screening programs to detect CMV in women during childbearing periods are not practical and cost-effective [28]. Therefore, development of a vaccine to prevent congenital CMV infection was listed as a top priority by the Institute of Medicine of the National Academy of Sciences [29]. Surgical management of these patients was not different from the remaining 29 patients presented with the same clinical conditions. All of them showed a smooth post-operative period.

CONCLUSION

Congenital CMV infection is likely to be a leading cause of neonatal gastrointestinal surgical conditions. Further studies of a greater number of neonates are needed.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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