

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

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Case 25-2003: A Newborn Boy with Petechiae and Thrombocytopenia

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PRESENTATION OF CASE

A newborn boy was admitted to a special-care nursery because of petechiae and thrombocytopenia.

The boy had been delivered at this hospital at 39 weeks' gestation to a 32-year-old woman who had had premature rupture of the membranes 16 hours before delivery. A single dose of penicillin was administered to the mother before vacuum-assisted delivery. The Apgar score was 9 at one minute and at five minutes. A diffuse petechial rash, most prominent on the face and trunk, was noted at delivery, and the baby was transferred to a newborn nursery.

The mother had never smoked, and she had not consumed alcohol after learning of the pregnancy. Prenatal serologic tests were negative for hepatitis B surface antigen and syphilis, positive for antibodies to rubella and for IgG antibody to cytomegalovirus (CMV; 63 arbitrary units), and equivocal for IgM antibody to CMV (1 arbitrary unit; <0.9 unit is a negative result, and >1.1 units a positive result). Ultrasonographic examination of the fetus at approximately 20 weeks' gestation revealed a focus of echogenicity within the heart and a hyperechoic bowel. Amniocentesis revealed that the chromosomes and the level of alpha-fetoprotein were normal; the fetal cells were negative for mutations in the cystic fibrosis gene. The estimated risk of Down's syndrome was 1 in 85. The mother did not have a history of febrile illness, genital lesions, or rash during the pregnancy. The family history was unremarkable on both the maternal and the paternal sides.

The infant's temperature was 36.6°C, the pulse 110 beats per minute, and the respiratory rate 48 breaths per minute. The blood pressure was 60/40 mm Hg. The weight was 2.29 kg (below the 10th percentile), the length 46 cm (between the 10th and 25th percentiles), and the head circumference 33 cm (at the 25th percentile).

On physical examination, the infant appeared well and comfortable; his features were not dysmorphic, and he was not in respiratory distress. Multiple petechial lesions were present on his face, trunk, and arms and legs and were especially numerous at the site on the head where the vacuum cup had been placed (Fig. 1). No lymphadenopathy was found. The anterior fontanelle was open and flat. The eyes showed no microphthalmia, icterus, or cataracts; the retinas were not examined. The clavicles were intact, and the lungs were clear. The heart sounds were normal. The abdomen was soft; the spleen

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Figure 1. Photograph of the Patient, Showing Petechiae on the Forehead.

was palpable 2.5 to 3.0 cm below the left costal margin, and the liver edge 3.0 cm below the right costal margin. The arms and legs were well perfused. Muscle tone was good throughout, with appropriate Moro's and sucking reflexes.

For several hours in the nursery, the infant's heart rate was in the range of 100 to 110 beats per minute, with occasional drops to 85 beats per minute. The arterial oxygen saturation occasionally declined from 95 percent or more to about 85 percent. The results of laboratory tests are given in Table 1. The levels of urea nitrogen, creatinine, total protein, triglyceride, aspartate aminotransferase, and alanine aminotransferase were normal. Examination of a peripheral-blood smear disclosed hypochromia (++) with macrocytosis, polychromasia (+), and teardrop cells. Specimens of blood, cerebrospinal fluid, and urine were obtained for culture, and ampicillin, tobramycin, and acyclovir were given. Breast-feeding was begun. The next day, the oxygen saturation ranged from 93 to 98 percent while the patient was breathing ambient air.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. John F. Modlin: May we see the prenatal radiologic studies and the clinical photographs?

Dr. Susan A. Connolly (Radiology): An intracardiac focus of echogenicity, which represents a small amount of calcification, usually in the papillary muscle, was visible on a cross-section image of the fetal chest showing the oblique four-chamber view of the heart. This finding can be a normal variant; it is seen in 5 percent of normal fetuses on second-trimester scans. However, it has been associated with an approximately doubled risk of Down's syndrome. The hyperechoic bowel, which was best seen on an oblique transverse image of the abdomen, is a find-

ing associated with infection with toxoplasma, CMV, togavirus (the agent that causes rubella), and herpes simplex virus and with increased risks of Down's syndrome, cystic fibrosis, bleeding, and growth retardation.

Dr. Stephen Walsh (Infectious Disease Unit): We were asked to see the infant the day he was born. There was a diffuse, macular, petechial eruption on his face but no pustules or vesicles (Fig. 1).

Dr. Modlin: This newborn infant had intrauterine growth retardation and shortly after birth was found to have hepatosplenomegaly, thrombocytopenia, and hyperbilirubinemia. It is helpful to begin by considering the broad categories of conditions associated with thrombocytopenia in newborns (Table 2).

Maternal antiplatelet antibodies are an important cause of thrombocytopenia in newborns, but their presence is not accompanied by hepatosplenomegaly or intrauterine growth retardation. There are no features of this case that suggest the presence of structural birth defects such as absent radii or a large hemangioma (the Kasabach–Merritt syndrome), and the complete blood count is not consistent with the presence of congenital leukemia. There are several metabolic diseases and other genetic disorders, such as Fanconi's anemia and the Wiskott–Aldrich syndrome, that may be manifested as neonatal thrombocytopenia, but usually not on the first day of life. This quick process of elimination leaves infection as the probable cause of the infant's thrombocytopenia. Early-onset bacterial sepsis was appropriately considered in this case, and the infant underwent a workup for sepsis and received broad-spectrum antibiotics. However, there were no risk factors for neonatal sepsis, such as maternal fever, chorioamnionitis, or premature labor. The normal white-cell count and the relatively benign course of illness make this diagnosis even less likely.

The main clinical features in this case are most consistent with an infection acquired in utero. Table 3 lists the organisms causing intrauterine infections that might have some or all of the principal features seen in this case — namely, thrombocytopenia, hepatosplenomegaly, and intrauterine growth retardation.^{1–6} Table 3 also includes my best estimate of the current overall incidence of each of these infections and the likelihood that a child will have symptoms and signs at birth. CMV is the most common agent in the differential diagnosis and thus must be considered in any infant who is thought to

have an intrauterine infection. Congenital toxoplasmosis is the infection most likely to be confused with CMV infection, but population-based screening in the United States indicates that toxoplasmosis infects newborns much less often than CMV infection. There are also distinguishing clinical features; the rash observed in infants with congenital toxoplasmosis is usually maculopapular rather than petechial, and infants with toxoplasmosis have chorioretinitis more often than those with congenital CMV infection.

Vertically transmitted infection with the human immunodeficiency virus (HIV) has dropped from a peak of approximately 1600 cases in 1992 to fewer than 200 cases in 2000. In the United States, approximately 30 percent of HIV-infected infants who are not being breast-fed acquired the infection during gestation, but they usually have no symptoms at birth. The rare newborns with symptomatic HIV infection have had intrauterine growth retardation, hepatosplenomegaly, pancytopenia, diffuse leukoencephalopathy, and early-onset *Pneumocystis carinii* pneumonia and have died early in life.^{7,8}

In congenital rubella, the rash tends to be more purpuric than petechial, and cataracts and congenital heart disease are common.⁹ Neither of the latter findings is present in this patient. Congenital syphilis, which is rapidly declining in incidence in the United States, is strongly associated with drug use by the mother. Infants with congenital syphilis have a scaly, copper-colored, macular rash in the first weeks of life, as well as mucous-membrane lesions and evidence of osteochondritis. Intrauterine infections can occur with either herpes simplex virus or varicella-zoster virus, although the former is far more likely to cause postnatal disease after intrapartum exposure, and intrauterine infection with either virus is rare. In most reported cases, congenital infection with herpes simplex virus or varicella-zoster virus has resembled congenital CMV infection, but these cases have also involved unique vesicular skin lesions or cutaneous scarring and, in congenital varicella, hypoplasia of the limbs.^{10,11}

CMV is a ubiquitous human herpesvirus that is the most common cause of intrauterine infection, affecting approximately 1 percent of all newborn infants. The fetus may become infected if a woman has a primary infection during pregnancy or if she has reactivation of a latent infection that was acquired before pregnancy. Although as many as 2 percent of women who are seropositive for CMV before pregnancy will deliver an infected infant, it

Variable	2 Hours	6 Hours	Day 2
White-cell count (per mm ³)	13,300	18,300	19,100
Hematocrit (%)	54.8	59.6	52.3
Hemoglobin (g/dl)	18.2	19.2	17.6
Red-cell count (per mm ³)	5,530	5,900	5,240
Platelet count (per mm ³)	50,000	57,000	68,000
Mean corpuscular volume (μm ³)	99	101	100
Mean corpuscular hemoglobin (pg/red cell)	32.9	32.5	33.5
Mean corpuscular hemoglobin concentration (g/dl)	33.1	32.2	33.6
Red-cell-distribution width (%)	19.5	19.2	19.6
Differential count (%)			
Neutrophils	34		59
Lymphocytes	50		27
Monocytes	7		7
Eosinophils	1		
Band forms	7		5
Myelocytes			2
Blasts	1		
Prothrombin time (sec)†			20.1
Partial-thromboplastin time (sec)‡			31.4
Total bilirubin (mg/dl)			4.5
Phosphorus (mg/dl)			4.1
Magnesium (mmol/liter)			0.65
Cerebrospinal fluid§			
Red cells			31,750
Neutrophils (%)			51
Lymphocytes (%)			39
Monocytes (%)			9
Eosinophils (%)			1

* To convert the value for total bilirubin to micromoles per liter, multiply by 17.1. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the value for magnesium to milliequivalents per liter, divide by 0.5.

† The normal range is 10.2 to 15.4 seconds.

‡ The normal range is 25.3 to 48.3 seconds.

§ Cells were measured in the fourth tube of fluid.

is very rare for such infants to have any clinical symptoms.^{12,13} In contrast, about 15 percent of infants born to women with primary infection have clinical disease that ranges from mild to severe.¹⁴⁻¹⁶

Table 2. Conditions Associated with Neonatal Thrombocytopenia.

Category	Condition
Maternal antiplatelet antibodies	Alloimmune thrombocytopenia (anti-human platelet antibodies) Idiopathic thrombocytopenic purpura Systemic lupus erythematosus Drug-induced antiplatelet antibodies
Congenital abnormalities	Thrombocytopenia with absent radii Large hemangioma (Kasabach–Merritt syndrome) Congenital leukemia
Metabolic diseases	Methylmalonicacidemia Ketotic glycinemia Isovalericacidemia Holocarboxylase synthetase deficiency
Other genetic disorders (selected)	Fanconi’s anemia Wiskott–Aldrich syndrome Trisomy 13, 18, or 21
Infections	Bacterial sepsis Intrauterine viral infection or toxoplasmosis Congenital syphilis

Table 3. Incidence of Selected Intrauterine Infections (per 100,000 Births) in the United States.

Infectious Agent	Symptomatic Disease at Birth		Reference
	Overall	<i>no. per 100,000 births</i>	
Cytomegalovirus	1000	100	Spagno, ¹ Weller and Hanshaw ²
Toxoplasma gondii*	8	<1	Guerina et al. ³
Human immunodeficiency virus†	2	<1	Eberhardt et al. ⁴
Rubella virus	<1	<1	
Herpes simplex virus	<1	<1	
Varicella–zoster virus	<1	<1	
Syphilis‡	13	4	Centers for Disease Control and Prevention, ⁵ Reyes et al. ⁶

* The data are based on the screening of newborns in New England.
 † The data are based on an estimated 200 infants infected with the human immunodeficiency virus per annum and a 30 percent rate of intrauterine transmission.
 ‡ The data are based on 2000 surveillance data and a 75 percent rate of asymptomatic infection at birth.

Most primary CMV infections in pregnancy occur in the early child-bearing years, when the rate of sexual transmission is high. The mother of this infant was 32 years old, well beyond the age range normally associated with primary CMV infection. It is interesting to speculate that during pregnancy, this previously seronegative woman may have acquired the infection from an older child who had acquired the infection in a day-care center. The rate of CMV seroconversion in women with at least one child at home is about twice as high as it is in women without children in the household.¹⁷ Furthermore, horizontal transmission is responsible for the high prevalence of infection among toddlers and preschool children who attend day-care centers.¹⁸

To summarize, the clinical and laboratory features suggest that this infant has acquired a vertically transmitted infection in utero. Consideration of both the epidemiologic and clinical data makes CMV infection the likely cause, but I cannot rule out toxoplasmosis, rubella, or infection with herpes simplex virus, varicella–zoster virus, or even HIV from the available information. I would approach the diagnosis in two steps, looking first for evidence of CMV infection and then testing for the other agents only if CMV infection appears unlikely. Isolation of CMV in cell culture remains the diagnostic standard. The virus can be isolated from several sources, but urine is the best specimen because of the high titer of virus that is invariably present. Many laboratories use one or more techniques to enhance or speed the identification of virus in cell culture; one such technique is the use of shell vials and monoclonal antibodies directed against early CMV antigens.

Dr. Nancy Lee Harris: Dr. Catlin, you cared for this patient in the newborn nursery. Would you give us your impressions before the diagnostic procedure?

Dr. Elizabeth A. Catlin (Pediatrics): My colleagues and I considered the causes of neonatal thrombocytopenia that Dr. Modlin has discussed and focused primarily on infection. Congenital CMV infection seemed most likely, given the combination of findings.

CLINICAL DIAGNOSIS

Congenital cytomegalovirus infection.

DR. JOHN F. MODLIN’S DIAGNOSIS

Congenital cytomegalovirus infection or another infection vertically transmitted in utero.

DIAGNOSTIC DISCUSSION

Dr. Harris: The diagnostic procedures were both imaging studies and a laboratory test.

Dr. P. Ellen Grant: Cranial ultrasonography was performed on the infant's first day of life. A coronal image at the level of the third ventricle showed cystic areas in the region of the germinal matrix at the caudothalamic groove. In a more posterior region of the brain, at the level of the atria of the lateral ventricle, there were multiple periventricular foci of echogenicity, which were thought to represent calcifications. On cranial computed tomographic scanning, the echogenic foci were confirmed to be areas of calcification; many areas of calcification can be seen in a periventricular location (Fig. 2A). The distribution of these lesions is typical of CMV infection, which has a predilection to involve the rapidly multiplying cells of the germinal matrix. On magnetic resonance imaging, an abnormal gyral folding pattern (affecting the right hemisphere more than the left) is visible, and in the affected areas, the junction between the gray matter and the white matter is irregular (Fig. 2B) — these findings are consistent with the presence of diffuse polymicrogyria. In the occipital regions, small periventricular pseudocysts are also evident. The cerebellum is hypoplastic.

The findings on imaging — calcifications that are predominantly periventricular, periventricular pseudocysts, polymicrogyria, and cerebellar hypoplasia — are almost pathognomonic for CMV infection. In addition, they tend to rule out toxoplasmosis, which is associated with enlarged ventricles without cortical malformations, as well as other congenital infections.

Dr. Robert S. Makar: The laboratory test used in this case was a shell-vial assay for CMV. The shell-vial assay is a variant of routine culture methods used to detect CMV in clinical specimens. In routine culture, CMV infection of cultured fibroblasts results in a characteristic cytopathic effect. Although the appearance of the cytopathic effect is a sensitive marker of viral infection, it can take several days to occur, depending on the viral titer in the clinical specimen. In contrast, with the shell-vial assay, virus can be detected within 24 hours after inoculation.¹⁹ In brief, glass coverslips bearing the cultured cells are placed in vials containing culture medium. The vials are inoculated with the specimen and then centrifuged at low speed to facilitate viral adsorption.²⁰ Viral infection is then detected by indirect

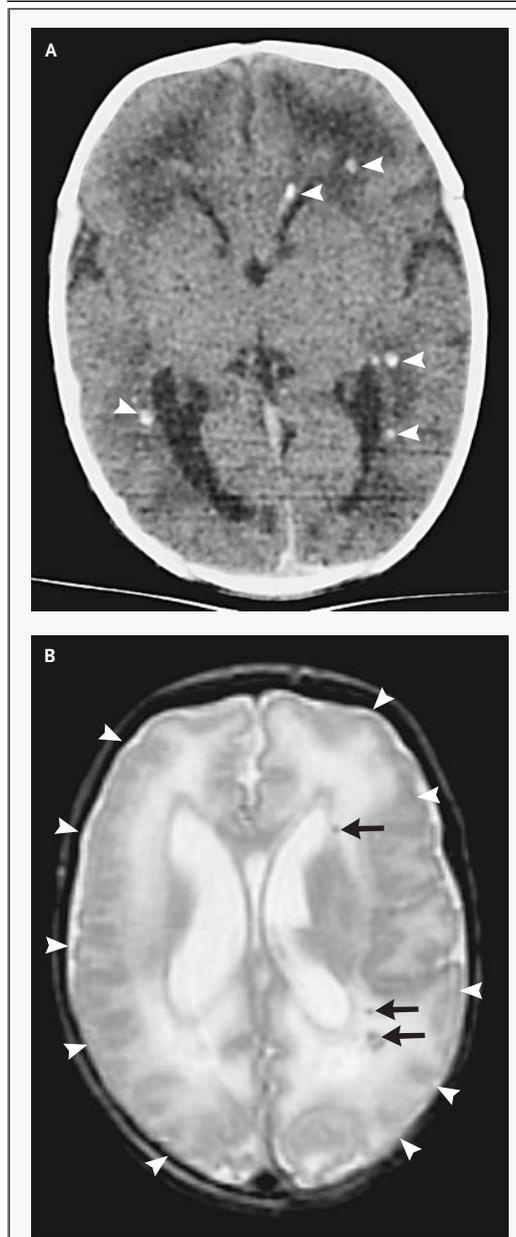


Figure 2. Cranial Imaging Studies.

An axial CT image of the cranium, obtained without the use of contrast material (Panel A), shows multiple punctate, periventricular foci of calcification (arrowheads). An axial image from a T₂-weighted MRI study (Panel B) shows multiple regions of abnormal gyral folding (arrowheads), a finding consistent with the presence of polymicrogyria. The punctate foci of decreased T₂ signal (arrows) correspond to calcifications, which are better seen on the CT scan. The white matter has an abnormally increased T₂ signal, and the ventricles are enlarged.

immunofluorescence for immediate-early antigens in the nuclei of the cultured cells. This patient's urine was floridly positive for CMV according to the shell-vial assay (Fig. 3).

Many tests are available for the diagnosis of CMV infection, but not all of them are reliable for the diagnosis of congenital infection. Detection of CMV antigenemia is a sensitive test for CMV infection in immunocompromised adults but has not been validated as a test for congenital CMV. Serologic tests for fetal IgG and IgM antibodies against CMV are difficult to interpret. Since IgG antibodies are passively transferred from mother to fetus, a positive anti-CMV IgG titer in fetal blood is not meaningful. Anti-CMV IgM antibodies do not cross the placenta, and their presence in cord blood suggests congenital infection. However, the sensitivity and specificity of currently available tests for IgM antibodies do not yet match those of viral-culture methods or polymerase-chain-reaction (PCR) assays for viral genetic material.¹ Thus, the diagnosis of congenital CMV infection hinges on the detection of virus by one of the latter two methods. Clinical specimens should be obtained within two weeks after birth to allow congenital and perinatal infections to be distinguished from one another.

Prenatal diagnosis of congenital CMV infection can be offered to women in whom seroconversion occurs during pregnancy. The isolation of virus or

viral DNA from amniotic fluid is the most reliable measure of congenital infection.¹ However, a negative result may not rule out infection, even when the sample of amniotic fluid is obtained after 20 weeks of gestation,²¹ and a positive result does not necessarily correlate with symptomatic infection.²² A recent study suggests that a high CMV load in the amniotic fluid on quantitative PCR is correlated with symptomatic infection²³ and thus may be useful as a prognostic tool in congenital CMV infection.

Dr. Harris: As is the routine when an infant is born ill, the placenta was examined in this case, and I would like to ask Dr. Drucilla Roberts to describe the findings.

Dr. Drucilla J. Roberts: The placenta was a small, singleton placenta; it weighed 310 g (below the 10th percentile for 39 weeks' gestation) and was discolored (greenish-brown) by meconium pigment. At least 50 percent of the villi were avascular, with open maternal vascular spaces (Fig. 4). This finding represents vascular compromise from the fetal (not maternal) circulation to the placenta.²⁴

The pathological differential diagnosis of avascular villi (Table 4) includes chronic villitis, either active or healed.²⁵ Chronic villitis, which is seen in up to 10 percent of all placentas examined histologically, is characterized by a maternal inflammatory infiltrate, typically mononuclear, in the villi. Most cases are thought to be due to a maternal factor (perhaps an immune response to the fetal allograft). A small number of cases are due to transplacental infection, with CMV being the most common agent.

The histopathological features of CMV placentitis include lymphoplasmacytic villitis, sclerosis of the villous capillaries, chorionic vessel thromboses, necrotizing villitis, hemosiderin deposition in the villous stroma, and immature nucleated fetal red cells in the blood vessels and viral inclusions (seen in approximately 10 percent of cases).²⁶ In the infant in the current case, there was no active chronic villitis, none of the features of an active CMV placentitis were present, and immunohistochemical stains for CMV antigen were negative.²⁷

Infants with a remote transplacental CMV infection often have nonspecific findings of villous sclerosis and chorionic vascular thromboses, and the weight of their placentas may be below the 10th percentile. The placental pathological findings in this case are consistent with a CMV villitis that developed at least two weeks before birth and possibly earlier and that has scarred, leaving the avascular sclerotic villi.

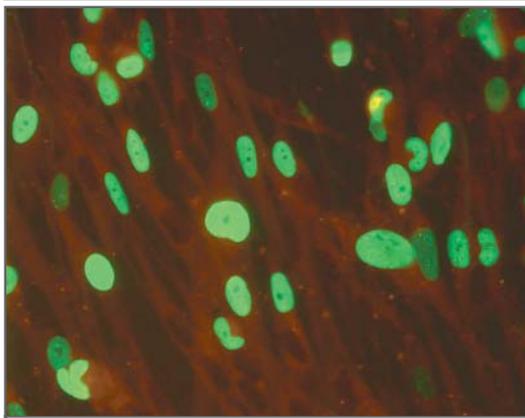


Figure 3. Shell-Vial Assay for Cytomegalovirus (CMV) (Immunofluorescence Stain, $\times 400$).

Fibroblasts inoculated with the patient's urine show apple-green nuclear staining with antibody to CMV immediate-early antigen, indicating CMV infection. The assay was performed with reagents obtained from Chemicon International.

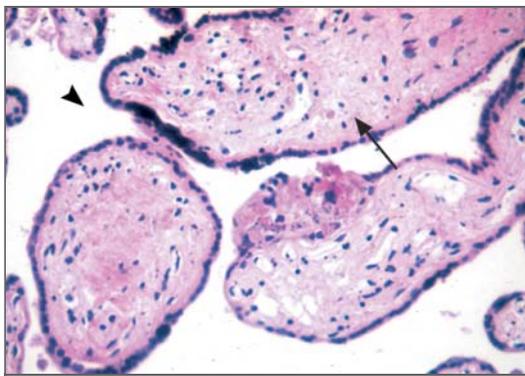


Figure 4. Histologic Section of the Placenta (Hematoxylin and Eosin, x250).
Avascular villi (arrow), with open maternal vascular spaces (arrowhead), are visible.

Table 4. Pathological Differential Diagnosis of Avascular Villi.

Thrombophilia
Sepsis
Inherited thrombophilia (e.g., factor V Leiden)
Flow-related disorder
Fetal heart failure
Anatomical anomaly
Tight true knot of the umbilical cord
Membranous or velamentous vessels
Endothelial injury
Toxic exposure
Prolonged exposure to meconium
Inflammatory injury
Fetal inflammatory infiltrate as seen in association with acute chorioamnionitis
Chronic villitis

Dr. Harris: Since we assumed that the diagnosis in this case would not be a problem for Dr. Modlin, I asked him to tell me his diagnosis before the conference and then invited him to discuss current issues in the management of congenital CMV infection.

DISCUSSION OF MANAGEMENT

Dr. Modlin: The case under discussion is representative of the approximately 10 percent of CMV-infected newborns who have clinical evidence of disease in the neonatal period. The severity of the infection appears to be related to the age of the fetus at the time of the infection: those infected during the first trimester have relatively severe consequences, whereas those infected during the third trimester may have no symptoms. The spectrum of signs and symptoms includes premature delivery, intrauterine growth retardation, microcephaly, jaundice, petechiae, hepatosplenomegaly, thrombocytopenia, indirect and direct hyperbilirubinemia, and other signs of mild hepatitis (Table 5).

The mortality rate is approximately 20 percent. For those who survive, the hematologic abnormalities, hepatitis, and other manifestations not involving the central nervous system resolve within weeks to months after birth, despite ongoing shedding of the virus, which persists for months to years after birth.²⁸ However, about 60 percent of these infants have sensorineural hearing deficits, and in about 70 percent microcephaly, seizures, motor abnormalities, developmental delay, or other cognitive impairments occur.²⁹ Overall, 90 percent of the surviving

infants will have either a sensory deficit or cognitive impairment.

Although the initial insult occurs in utero, the developing central nervous system remains vulnerable to damage from persistent viral replication after birth, and thus effective antiviral therapy given after birth may reduce the severity of the neurologic damage and improve the long-term outcome.^{30,31} The first opportunity to test this hypothesis came with the development of ganciclovir, a derivative of acyclovir, which was the first antiviral agent capable of inhibiting CMV replication at clinically attainable concentrations. The Collaborative Antiviral Study Group of the National Institute of Allergy and Infectious Diseases recently completed a phase 3 trial of intravenous ganciclovir for symptomatic congenital CMV disease in infants.³² This challenging trial required the parents of infants with a devastating prognosis to accept random assignment to treatment with ganciclovir or no treatment and required the placement of a central venous catheter and twice-daily intravenous treatment. The infants who were randomly assigned to a six-week course of intravenous ganciclovir had significantly better hearing and more rapid resolution of hepatitis than the infants who were not treated.

These unequivocal results provide proof of concept and allow us to proceed to studies designed to optimize antiviral therapy for CMV-infected newborns. A planned Collaborative Antiviral Study Group trial will evaluate longer-term treatment with valganciclovir, a recently licensed prodrug that reaches serum concentrations similar to those of

Table 5. Selected Clinical and Laboratory Findings in 106 Infants with Symptomatic Intrauterine Congenital Cytomegalovirus Infection in the Neonatal Period.*

Finding	Incidence percent
Prematurity (gestation <38 wk)	34
Intrauterine growth retardation	50
Microcephaly	53
Jaundice	67
Petechiae	76
Purpura	13
Hepatosplenomegaly	60
Thrombocytopenia (platelet count <100,000 per mm ³)	77
Hemolytic anemia	51
Hyperbilirubinemia (total bilirubin level >4 mg/dl)†	69
Elevated alanine aminotransferase (>55 U/liter)	83

* The information is adapted from Azam et al.²¹

† To convert the value for bilirubin to micromoles per liter, multiply by 17.1.

ganciclovir when given orally. If this study shows that valganciclovir is effective in further reducing the morbidity associated with symptomatic congenital CMV infection, then it follows that treatment of the 90 percent of infected infants who have no symptoms at birth but who have a lower but well-documented risk of hearing loss than those with signs of infection at birth will be the target of further antiviral research.¹ In turn, this would raise a brand-new issue for those who study the feasibility and outcomes of newborn screening and perform cost-benefit analyses. At this moment, the future for the diagnosis and treatment of congenital CMV infections looks very promising.

Dr. Harris: Dr. Walsh will discuss the treatment decision that was made in the current case.

Dr. Walsh: We reviewed the published phase 2 data on the use of intravenous ganciclovir for congenital CMV infection³³ and contacted a colleague at the University of Alabama at Birmingham, who shared with us preliminary data from the phase 3 trial of ganciclovir.²⁹ The data were particularly encouraging with respect to the stabilization of hearing loss. We then discussed treatment options with

the parents of the infant in this case, and they opted to have their infant receive intravenous ganciclovir for six weeks. Therapy was completed without serious complications.

Dr. Harris: Dr. Casavant, you are this patient's primary care physician and have been working with the family during the administration of treatment at home. Would you discuss some of the issues and tell us how the patient is doing now?

Dr. David W. Casavant (Pediatrics): After the diagnosis was established, further evaluation showed mild CMV-associated chorioretinitis and profound hearing loss in the left ear. The ganciclovir treatment required placement of a central venous catheter and twice-weekly testing of blood samples to monitor the complete blood count for evidence of neutropenia or anemia, since ganciclovir is toxic to the bone marrow. One of the parents' chief problems during the first months after the infant's birth was the fear of other family members that they or their children might be infected by the infant. We tried to assure them that CMV infection is quite common and is not associated with problems in immunocompetent persons, when acquired after the neonatal period.

Although the literature forecasts a rather bleak picture for the patient's development, he has done remarkably well. At his most recent routine visit, he was approximately 22 weeks old and had only mild left-sided weakness and some resolving torticollis.

Dr. Harris: This patient was evaluated and followed by Dr. Krishnamoorthy. Dr. Krishnamoorthy, would you review the neurologic complications of congenital CMV infection and tell us about this patient's neurologic status and prognosis?

Dr. Kalpathy S. Krishnamoorthy: Neonates with CMV infection can be divided into three prognostic groups. Up to 95 percent of those with overt manifestations in the central nervous system (e.g., microcephaly, cerebral calcification, or chorioretinitis) have major neurodevelopmental sequelae; those with only systemic manifestations (e.g., jaundice, petechiae, or hepatosplenomegaly) are still at risk but have a slightly better prognosis; and those with neither central nervous system nor systemic manifestations have the best prognosis. However, even infants with no symptoms are at risk for developmental delay, microcephaly, motor deficits, and (most commonly) sensorineural hearing loss, which may not become apparent until late infancy or early childhood.³⁴ An important clinical point is that congenital CMV infection should be included in the

differential diagnosis of developmental delay associated with microcephaly and sensorineural hearing loss during infancy, even in the absence of neonatal manifestations of CMV infection.

Microcephaly is the most specific predictor of mental retardation and major motor disability. In a recent study,³⁵ the combination of microcephaly and abnormal findings on CT imaging carried the worst prognosis (mean IQ score, <50; major motor deficit in 75 percent of the patients); a normal head circumference and normal CT findings were associated with a good prognosis (mean IQ score, >90; no major motor deficit); and a normal head circumference and abnormal CT findings were associated with an intermediate prognosis (mean IQ score, 70 to 80; major motor deficit in 37 percent).

In view of the abnormalities seen on CT scanning in this infant, he falls into the intermediate prognostic group. We have seen him twice in follow-up, most recently when he was 14 weeks of age. His head circumference has stayed at the 25th percentile, which is in line with his overall size. He remains visually alert and sociable and has a good smile. Assessment of muscle tone shows diffuse, mild hypertonia that is manifested as prominent clenching of the fists and excessive arching of the

back. Left-sided sensorineural hearing loss persists, but the ophthalmologic findings remain normal. His prognosis remains uncertain.

Dr. Grant: The presence of polymicrogyria on the imaging studies suggests that the major injury to the fetal brain occurred somewhere between 20 and 25 weeks' gestational age. Would it have been possible to treat the mother when she seroconverted?

Dr. Modlin: The usual problem is detecting infection in the pregnant woman, because the majority of these infections are completely silent. Unfortunately, it is not clear that there is an effective and safe prenatal treatment for fetal CMV infection.

Dr. Casavant: Because of the mother's equivocal IgM response to CMV in the presence of IgG antibodies, the possibility of recent infection was discussed with her early in the pregnancy. However, there are no guidelines for treatment of CMV infection during pregnancy.

PATHOLOGICAL DIAGNOSIS

Congenital cytomegalovirus infection.

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