CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 4-2018: A Newborn with Thrombocytopenia, Cataracts, and Hepatosplenomegaly

Robert S. Baltimore, M.D., Katherine Nimkin, M.D., Katherine A. Sparger, M.D., Virginia M. Pierce, M.D., and Stanley A. Plotkin, M.D.

From the Departments of Pediatrics and Infection Prevention, Yale New Haven Children's Hospital, and the Departments of Pediatrics and Epidemiology, Yale School of Medicine and Yale School of Public Health, New Haven, CT (R.S.B.); the Departments of Radiology (K.N.), Pediatrics (K.A.S., V.M.P.), and Pathology (V.M.P.), Massachusetts General Hospital, and the Departments of Radiology (K.N.), Pediatrics (K.A.S.), and Pathology (V.M.P.), Harvard Medical School — both in Boston; and the Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (S.A.P.).

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PRESENTATION OF CASE

Dr. Madeleine I. Matthiesen (Medicine and Pediatrics): A newborn boy was transferred to the neonatal intensive care unit (ICU) of this hospital because of thrombocytopenia and abnormal results on an eye examination for red reflex and on a hearing screening.

The patient was born to a 27-year-old mother (gravida 2, para 2) by spontaneous vaginal delivery at another hospital after an uncomplicated gestation of 39 weeks 4 days. His mother had received prenatal care in Nigeria and had also been seen by an obstetrician in New England for one office visit at 24 weeks 4 days of gestation. At that appointment, results of an ultrasonographic survey of the fetal anatomy were normal, and antepartum screening tests for human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, and syphilis were negative. A maternal test for IgG antibodies to rubella virus was positive (>500 IU per milliliter; reference range for immunity, ≥9.9), as was a test for IgG antibodies to varicella–zoster virus. The maternal ABO blood type was O, Rh positive, and screening for antibodies to red cells was negative; hemoglobin electrophoresis revealed the presence of hemoglobin AS.

The mother traveled back to Nigeria before returning to New England at 34 weeks of gestation in anticipation of the birth. At delivery, meconium was present. The 1-minute and 5-minute Apgar scores were 7 and 8, respectively. The birth weight was 3.21 kg (54th percentile), the length 51 cm (72nd percentile), and the head circumference 33.5 cm (22nd percentile). The newborn had tremulous movements of the arms and legs, and the blood glucose level was reportedly 20 mg per deciliter (1.1 mmol per liter). He was admitted to the special care nursery at the other hospital, where intravenous fluids that contained dextrose were administered and breast-feeding was initiated; the blood glucose level normalized.

On examination of the newborn the following day, the vital signs were normal. Scattered petechiae were present on the face, and an eye examination revealed that the red reflex was absent in the left eye and decreased in the right eye. The platelet count was 18,000 per cubic millimeter (reference range, 150,000 to 450,000). Newborn blood-spot screening tests (a panel of tests for multiple congenital diseases, primarily inborn errors of metabolism) revealed the presence of hemoglobin FAS and were otherwise negative. On a hearing screening, no auditory brain-stem response was detected when the test sound was presented to either ear. A polymerase-chain-reaction (PCR) assay for cytomegalovirus DNA in the urine was negative, as was a maternal rapid plasma reagin test. At 48 hours of age, the patient was transferred to the neonatal ICU of this hospital for further evaluation and treatment.

The history was obtained from the patient's mother. She reported that she was unsure whether the newborn responded to her voice or other sounds. She had received treatment for malaria during the first trimester of pregnancy and had received amoxicillin–clavulanate for a respiratory tract infection during the early part of the third trimester. The family lived in an urban area of Nigeria, where the parents worked in the banking sector and employed a live-in nanny to help care for the patient's 3-year-old sister. They did not have pets and had not noted rodents or other pests in their home. The patient's mother, father, and sister were healthy. During the mother's previous pregnancy, prenatal care had taken place exclusively in Nigeria; the child had been delivered in the southeastern United States, and the mother and child had traveled back to Nigeria shortly after the birth. Otherwise, the mother had not traveled internationally; the father had traveled to China for business during the past year.

Table 1. Laboratory Data.

Variable	Reference Range, Age-Adjusted*	On Admission
White-cell count (per mm^3)	9400–34,000	13,710
Differential count (%)		
Neutrophils	53–62	45
Lymphocytes	21–34	41
Monocytes	4–11	5
Eosinophils	0–8	6
Myelocytes	0	2
Metamyelocytes	0	1
Platelet count (per mm^3)	150,000–450,000	14,000
Red-cell distribution width (%)	11.5–16.0	23.1
Reticulocyte count (%)	0.5–2.5	7.3
Description of peripheral-blood smear		1+ polychromasia; burr cells present
Sodium (mmol/liter)	135–145	144
Potassium (mmol/liter)	4.0–5.6	6.0
Chloride (mmol/liter)	98–106	105
Carbon dioxide (mmol/liter)	19–22	18
Anion gap (mmol/liter)	3–17	21
Bilirubin (mg/dl)†		
Total	2.0–15.0	1.3
Direct	0.5–3.5	0.4
Protein (g/dl)		
Total protein	6.0–8.3	5.8
Albumin	3.3–5.0	3.4
Globulin	1.9–4.1	2.4
Shell-vial culture for cytomegalovirus in saliva	Negative	Negative

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted and are for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
† To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

On examination in the neonatal ICU, the newborn was awake and appeared well, and the vital signs were normal. Scattered petechiae were present on the face. The red reflex was absent in both eyes. A systolic ejection murmur (grade 2/6) was heard in the left upper chest. Mild hepatosplenomegaly was present. Increased muscle tone was present in the arms and legs, and intermittent, suppressible, rapid shaking movements occurred in the arms. The remainder of the examination was normal. The hemoglobin level, hematocrit, red-cell count, red-cell indexes, and blood levels of glucose, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were normal, as were the results of coagulation tests; other laboratory test results are shown in Table 1. A blood sample was obtained for culture. Ampicillin and gentamicin were administered intravenously, and platelets were transfused.

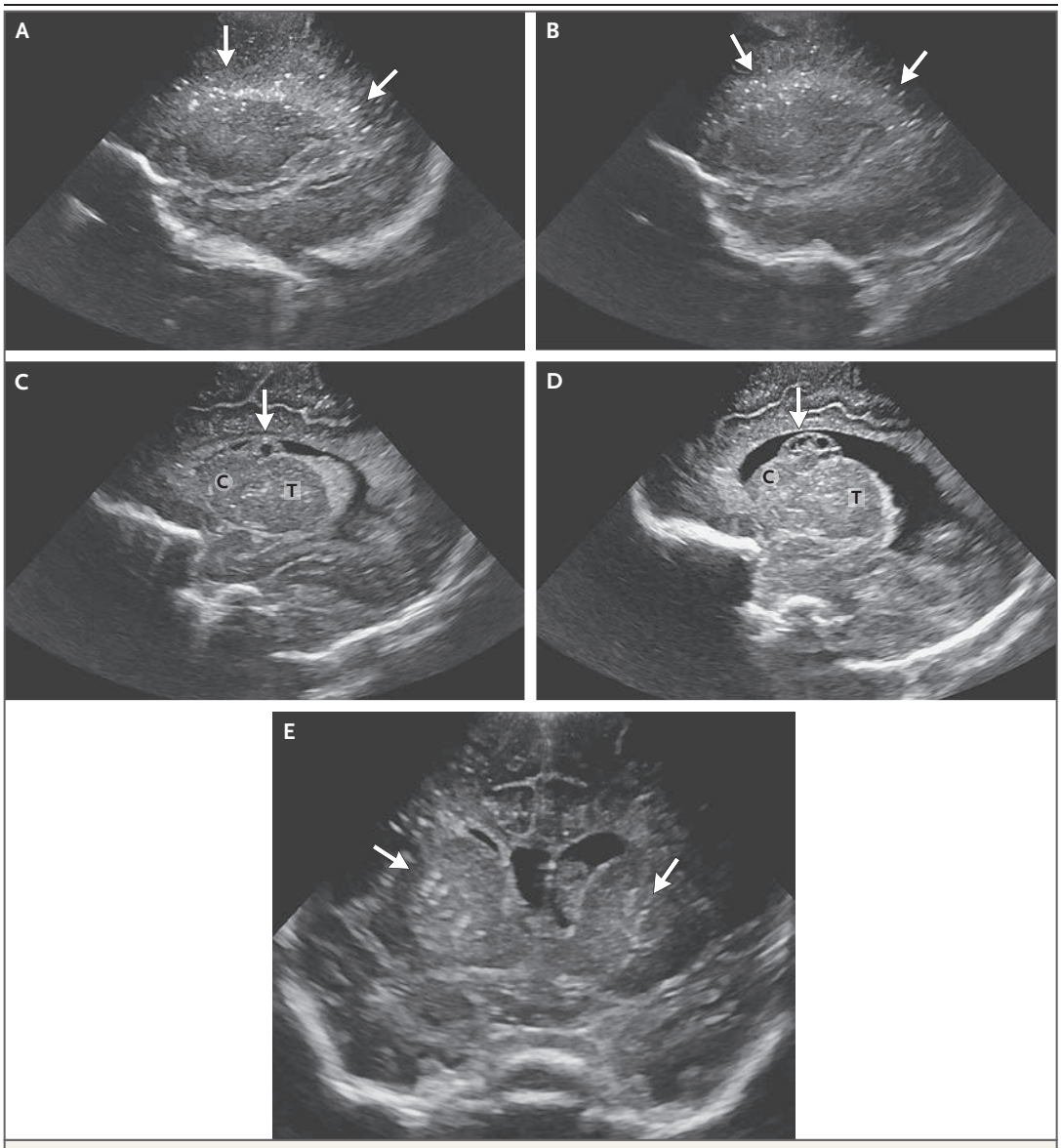

Figure 1. Cranial Ultrasound Images.

Right and left sagittal images (Panels A and B, respectively) show multiple punctate, echogenic foci in the periventricular white matter, a finding consistent with calcifications (arrows). Additional right and left sagittal images (Panels C and D, respectively) show complex subependymal cysts in the caudothalamic grooves bilaterally that are larger on the left side than on the right side (arrows). C denotes caudate, and T thalamus. There is mild dilatation of the left lateral ventricle. An anterior coronal image (Panel E) shows linear, branching, echogenic foci in the basal ganglia bilaterally, a finding consistent with lenticulostriate vasculopathy (arrows).

Dr. Katherine Nimkin: Cranial ultrasonography was performed through the anterior fontanelle (Fig. 1). Sagittal images showed multiple punctate, echogenic foci in the periventricular white matter bilaterally, a finding consistent with calcifications. Punctate calcifications were also present in the basal ganglia. Complex subependymal cysts were seen in the caudothalamic grooves bilaterally; these were larger on the left side than on the right side. There was mild dilatation of the left lateral ventricle. Linear, branching, echogenic foci were present in the basal ganglia bi-

laterally, a finding consistent with lenticulostriate vasculopathy.

Intracranial calcifications in the neonate may result from a variety of conditions. Congenital infection is usually the first diagnostic consideration; other causes include hypoxic–ischemic injury, neoplasm, and genetic disorders.[1] The pattern of calcification in the periventricular white matter and basal ganglia in this patient is suggestive of congenital infection.[2] Subependymal cysts, which were seen in this case, may result from hemorrhage, hypoxic–ischemic injury, or congenital infection.[3] These cysts may also result from rare metabolic and genetic disorders and may be seen in healthy newborns. Lenticulostriate vasculopathy is the presence of hyperechogenic vessels in the basal ganglia or thalami on cranial ultrasonography. This finding may be seen in healthy infants; however, it has been associated with infectious and noninfectious conditions and is most likely a nonspecific marker of perinatal brain injury.[4]

In this patient, chest radiography (Fig. 2A) revealed a normal heart and mediastinum and clear lungs. There were thin, transverse lucent bands in the proximal humeral metaphyses bilaterally. Metaphyseal lucent bands in the neonate may result from changes associated with chronic stress or from congenital infections. Other causes of metaphyseal lucent bands include metastatic neuroblastoma and leukemia. Abdominal ultrasonography confirmed the finding of hepatosplenomegaly (Fig. 2B).

Dr. Matthiesen: A slit-lamp examination revealed lamellar cataracts in both eyes, with anterior capsular plaque in the left eye. A diagnostic test was performed.

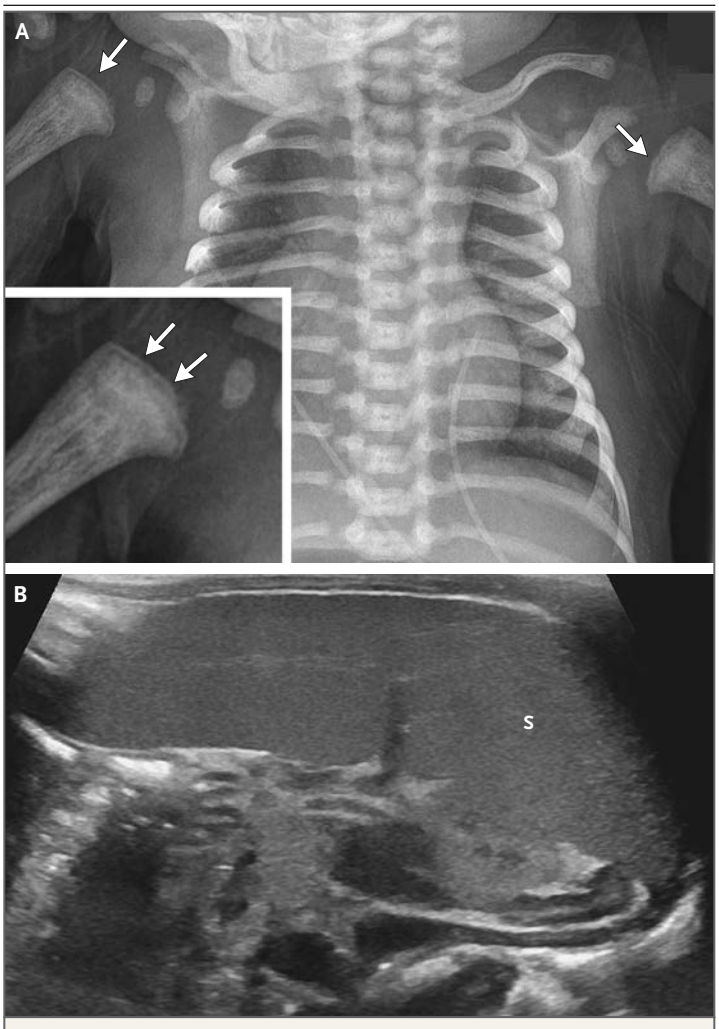

Figure 2. Chest Radiograph and Abdominal Ultrasound Image.
A chest radiograph (Panel A) is normal except for the presence of transverse lucent bands in the proximal humeral metaphyses bilaterally (arrows). The inset shows a magnified image of the right shoulder. An abdominal ultrasound image (Panel B) confirms the finding of splenomegaly. The spleen (S) measures 6.5 cm in length (normal length, ≤6).

DIFFERENTIAL DIAGNOSIS

Dr. Robert S. Baltimore: This newborn boy was transferred to the neonatal ICU of this hospital 48 hours after birth because of thrombocytopenia, an absent red reflex, and deafness. The birth weight and length were unremarkable, but the head circumference was in the 22nd percentile, a finding that suggests microcephaly relative to the body size. After the patient was transferred to this hospital, hepatosplenomegaly, cataracts, and a thin lucent band in the proximal metaphysis of each humerus were also noted, and cranial ultrasonography revealed evidence of calcifications in the periventricular white matter and basal ganglia, subependymal cysts, and lenticulostriate vasculopathy.

Taken together, these abnormalities are most likely due to a congenital infection. The acronym TORCH (toxoplasmosis, other [syphilis, varicella, parvovirus B19 infection, HIV infection], rubella, cytomegalovirus infection, and herpes simplex virus infection) is often used to identify possible congenital infections,[5] and at some hospitals, newborns with anomalies are evaluated with

laboratory tests that are referred to as "TORCH titers." I avoid the term TORCH, because thinking of the infections included in this acronym as causes of a single syndrome may lead one to ignore the important differences among the infections and therefore may encourage an unfocused approach to diagnostic testing. In assessing an infant with a suspected congenital infection, I consider the findings that are moderately specific for each infection in order to distinguish among them.[6] For example, congenital syphilis is often associated with irregularity of the long-bone metaphyses; although this patient had metaphyseal abnormalities, a maternal rapid plasma reagin assay was negative at delivery, and thus syphilis can be ruled out. On the basis of the clinical features present in this newborn, three congenital infections should be considered: cytomegalovirus infection, toxoplasmosis, and rubella.

CYTOMEGALOVIRUS INFECTION

Approximately 0.5 to 1% of infants in the United States are born with congenital cytomegalovirus infection, but only 10% of affected newborns have signs or symptoms of infection at birth. In symptomatic infants, characteristic features include thrombocytopenia, hepatosplenomegaly, periventricular intracranial calcifications, and hearing loss, all of which were present in this patient. However, a PCR assay for cytomegalovirus DNA in the urine was negative. Since this is a highly sensitive test,[7] congenital cytomegalovirus infection can be ruled out in this case.

TOXOPLASMOSIS

Features that are associated with congenital toxoplasmosis include a history of ingestion of raw muscle meat or contact with cats or cat litter in the mother, as well as chorioretinitis and the presence of intracranial calcifications scattered throughout the brain parenchyma in the newborn.[8] In this case, neither dietary risk factors nor cat contacts were identified in the maternal history. The newborn had intracranial calcifications, but they were periventricular rather than diffuse. Although no retinal abnormalities were noted, the presence of cataracts may have made them difficult to observe.

A diagnosis of congenital toxoplasmosis is usually established by means of serologic testing. Although the results of such testing are not specifically reported in this case, the newborn blood-spot screening tests in Massachusetts (performed as part of the New England Newborn Screening Program) include an antibody test for toxoplasmosis. The newborn blood-spot screening tests were negative apart from the detection of hemoglobin FAS; these results indicate that antibodies to *Toxoplasma gondii* were absent and thus rule out a diagnosis of toxoplasmosis.

RUBELLA

The abnormalities seen in this newborn — including cataracts, thrombocytopenia, bony abnormalities, and deafness — are consistent with the congenital rubella syndrome (Table 2).[9] Nevertheless, at first examination, the congenital rubella syndrome seems unlikely, because rubella virus is not currently present in the United States[10] and because the newborn's mother had immunity to rubella virus on prenatal testing. In the United States, women are typically tested for antibodies to rubella virus at their first prenatal visit, and positive results usually reflect previous immunization with the rubella vaccine. However, in this case, the test for antibodies to rubella virus was performed at 24 weeks 4 days of gestation, during the latter part of the second trimester. Therefore, it is possible that this patient's mother did not have immunity to rubella virus at the beginning of pregnancy and that acute rubella developed during the first trimester, which would allow ample time for a high concentration of IgG antibodies to rubella virus to develop by the time testing was performed. The fact that rubella virus is not present in the United States may be misleading, because the patient's mother spent the first trimester in Nigeria, where vaccination is not universal and rubella virus continues to circulate. Given that this newborn's syndrome is most consistent with the congenital rubella syndrome and that this diagnosis is not ruled out by the epidemiology of rubella or the laboratory data provided, I think the congenital rubella syndrome is the most probable diagnosis. I suspect the diagnostic test in this newborn was either a test for IgM antibodies to rubella virus in the blood or a PCR assay for rubella virus RNA in the blood or in affected tissue, and I suspect that at least one of the tests was positive.

Unfortunately, this patient's prognosis is poor. Microcephaly due to infection suggests poor development of the brain. This case resembles the unfortunate cases involving infants born to mothers with Zika virus infection; brain development is abnormal in those infants, and they are left with severe disabilities. In infants with the congenital rubella syndrome, cataracts and cardiac anomalies may be managed with surgery, and hearing loss with cochlear implantation. Infants with the congenital rubella syndrome have difficulty clearing the virus, and surveillance cultures or PCR assays may remain positive for many months; during that time, the infant may be a source of infection for persons who do not have immunity.

Dr. Virginia M. Pierce: Dr. Sparger, what was the clinical team's impression when you evaluated this patient?

Dr. Katherine A. Sparger: In this full-term infant who had early-onset thrombocytopenia that was severe (platelet count, <50,000 per cubic millimeter), we initially considered sepsis, congenital infection, disseminated intravascular coagulation, transplacental passage of maternal alloantibodies or autoantibodies, and other rare genetic and metabolic disorders as potential causes of the thrombocytopenia.[11] However, given the constellation of additional clinical findings — including hepatosplenomegaly, cataracts, abnormalities of the brain on ultrasonography, hearing loss, and metaphyseal lucent bands — congenital infection quickly rose to the top of our differential diagnosis, and cytomegalovirus infection, toxoplasmosis, and rubella were thought to be most consistent with the clinical presentation.

At the birth hospital, a PCR assay for cytomegalovirus DNA in the urine had been negative; at this hospital, shell-vial cultures for cytomegalovirus in the saliva and urine were also negative. We alerted the New England Newborn Screening Program of the suspicion of congenital infection in this patient, and the newborn blood-spot screening tests were expedited. Antibodies to *T. gondii* were absent. Although prenatal testing had shown maternal immunity to rubella, we were concerned that the high titer of IgG antibodies to rubella virus in the maternal blood sample that had been obtained at 24 weeks 4 days of gestation could reflect the recent development of rubella rather than immunity that predated pregnancy, and we considered the possibility that the development of rubella during early pregnancy could explain the clinical findings in the newborn.[12,13]

Table 2. Manifestations of the Congenital Rubella Syndrome.

Manifestation	Present in This Patient
Intrauterine growth retardation (low birth weight)	
Eye defects	
Cataracts	Yes
Glaucoma	
Retinopathy	
Microphthalmia	
Cardiac defects	
Patent ductus arteriosus	Yes
Peripheral pulmonary-artery stenosis	
Ventricular septal defect	
Myocardial necrosis	
Hearing impairment	Yes
Central nervous system defects	
Psychomotor retardation	
Microcephaly	Yes
Encephalitis	
Spastic quadriparesis	
Cerebrospinal fluid pleocytosis	
Mental disability	
Progressive panencephalitis	
Other manifestations	
Hepatomegaly	Yes
Hepatitis	
Thrombocytopenic purpura	Yes
Splenomegaly	Yes
Bone lesions	Yes
Interstitial pneumonitis	
Diabetes mellitus	
Psychiatric disorders	
Thyroid disorders	

CLINICAL DIAGNOSIS

Congenital rubella syndrome.

DR. ROBERT S. BALTIMORE'S DIAGNOSIS

Congenital rubella syndrome.

PATHOLOGICAL DISCUSSION

Dr. Pierce: Newborns with the congenital rubella syndrome shed rubella virus in the throat, nasopharynx, and urine. Because growth of the virus in cultured mammalian cell lines is relatively slow and cultivation and identification of the virus are labor-intensive, nucleic acid amplification tests have been developed to directly detect rubella virus RNA in clinical samples.[14,15] In this case, a throat swab, nasopharyngeal swab, and urine specimen were obtained on the third hospital day and submitted to the Centers for Disease Control and Prevention (CDC) for testing. A real-time PCR assay targeting a conserved sequence in the coding region of the rubella virus glycoprotein E1 gene detected rubella virus RNA in all three specimens.

On the basis of genetic differences in a larger sequence of the coding region of the glycoprotein E1 gene, the rubella virus is divided into two clades and 13 genotypes.[16] Such molecular epidemiologic categorization is a critical component of the global effort for rubella control and elimination, because it helps in tracking the spread of virus around the world and in characterizing changes in endemic strains over time. Using the genotyping protocol of the World Health Organization Global Measles and Rubella Laboratory Network,[17] the CDC determined that this patient's virus represented genotype 1G. This genotype has been found primarily in Africa in recent years, and the lineage containing this patient's virus is geographically restricted to Western Africa (Ivory Coast, Ghana, and Nigeria).[16]

In addition to direct viral detection, evidence of the production of antibodies to rubella virus in an infant can be used to establish a diagnosis of the congenital rubella syndrome.[18,19] Affected newborns produce IgM antibodies to rubella virus. These antibodies can usually be detected at birth with the use of a capture enzyme-linked immunosorbent assay; the level increases during the first 3 months of life and then declines over time. In this patient, a blood specimen obtained at 5 days of age was negative for IgM antibodies to rubella virus, but specimens obtained at 1 month and 2 months of age were positive.

At birth, tests for IgG antibodies to rubella virus cannot be used to distinguish between transplacentally acquired maternal antibodies and antibodies produced by the neonate. However, another means of establishing a diagnosis of the congenital rubella syndrome is showing that the level of IgG antibodies to rubella virus does not substantially decrease during the first few months of life, as the maternal antibodies decay.[20] In this infant, the level of IgG antibodies to rubella virus remained stable in blood specimens that were obtained at 5 days, 1 month, and 2 months of age; these findings indicate that IgG antibodies were produced by the infant. Finally, IgG antibodies to rubella virus that are produced by infants with congenital infection are typically of low avidity; therefore, a diagnosis of the congenital rubella syndrome can be established by detecting low-avidity antibodies in the blood after the maternal antibodies have waned. In this case, a maternal blood sample that was obtained just after delivery contained high-avidity IgG antibodies to rubella virus, whereas a blood specimen that was obtained from the infant at 3 months of age contained low-avidity IgG antibodies to rubella virus, a finding that further supports the diagnosis of the congenital rubella syndrome.

We are delighted to have Dr. Plotkin share his perspective on this patient's case in the context of the global epidemiology of the congenital rubella syndrome and the effect of vaccination on this disease. In the 1960s, Dr. Plotkin developed the rubella vaccine, which is now in use throughout the world.

HISTORICAL AND GLOBAL HEALTH PERSPECTIVE

Dr. Stanley A. Plotkin: This infant is very reminiscent of the babies I saw in Philadelphia during the 1964–1965 rubella epidemic.[21] The epidemic burgeoned throughout the United States, leading to at least 20,000 births associated with defects and many more abortions.[22-24] Because abortion was largely illegal then, we will never know how many were performed. However, I was able to estimate that, in Philadelphia, 1% of pregnancies during that period were complicated by rubella.[21]

I began to see that many infants born to mothers with rubella infection indeed had the congenital rubella syndrome.[25] The panoply of abnormalities was disheartening. The most severe was microcephaly, although some infants without that stark sign of brain damage later showed signs of intellectual disability. Patent ductus arteriosus was common, as were congenital cataracts. Deafness turned out to be the most common late manifestation of the congenital rubella syndrome. Thrombocytopenia owing to destruction of megakaryocytes, which was seen in this case, has been reported in about 30 to 60% of infants with the congenital rubella syndrome but usually disappears within weeks after birth.[26,27]

The results of worldwide use of the rubella vaccine have been gratifying but imperfect. The estimated number of cases of the congenital rubella syndrome worldwide is still approximately 100,000 per year.[28] Rubella and the congenital rubella syndrome have been eradicated from the Western hemisphere because of good vaccine coverage.[29,30] Unfortunately, although rubella has been controlled in many countries in Europe, opposition to vaccination in some countries has prevented the elimination of rubella, and there is much work to be done. In contrast, routine vaccination against rubella has just begun in some Asian countries, including India, Thailand, China, Japan, and Indonesia. Coverage in Africa is spotty, but a few countries have introduced the vaccine. In Nigeria, where this case originated, vaccination is limited to private providers, and coverage is less than 10%. It is anticipated that routine administration of the inexpensive measles–rubella vaccine will begin in Nigeria in 2021 (Papania MJ: personal communication).

Fortunately, there is a campaign to introduce the combined measles–rubella vaccine throughout the world, and all regions have goals to eradicate both diseases. The best strategy is a combination of complete coverage in the pediatric population to reduce circulation of the virus and postpartum vaccination of women to make them immune during their next pregnancies. Pediatric coverage must be high to prevent a paradoxical increase in exposure to rubella among seronegative women. Because the reproductive number (the indicator of infectiousness) of rubella is much lower than that of measles, one can hope for eradication of rubella even before that of measles.

Dr. Pierce: Dr. Matthiesen, would you tell us what happened with this infant?

Dr. Matthiesen: Although no effective antiviral therapy is available for the treatment of the congenital rubella syndrome, this patient has received multidisciplinary supportive care. Transfusion-dependent thrombocytopenia persisted for nearly 3 months. An echocardiogram showed a small patent ductus arteriosus. The cataracts were removed when the patient was 6 weeks of age, and contact lenses were prescribed. After additional testing confirmed profound sensorineural hearing loss, the patient was given hearing aids. A gastrostomy tube was placed because of inadequate caloric intake. The patient had abnormal movements but no seizures, and he received intensive physical, occupational, and speech therapy during hospitalization and after discharge.

When the patient was 6 months of age, he and his mother returned to Nigeria. At that time, PCR testing of a nasopharyngeal swab from the infant revealed persistent shedding of the rubella virus, which had important implications for his reentry into a population that does not have a high level of immunity. The patient is scheduled to return to this hospital for placement of cochlear implants when he is 12 months of age.

Dr. Laura E. Riley (Obstetrics and Gynecology): Unfortunately, an important opportunity to prevent the congenital rubella syndrome in this infant was missed. When his mother presented for delivery of her first child in the United States 3 years earlier, her rubella serostatus should have been determined and the rubella vaccine should have been administered during the postpartum period.

FINAL DIAGNOSIS

Congenital rubella syndrome.

This case was presented at Pediatric Grand Rounds.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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